

(57) Abstract: Disclosed are compounds of formula (I), and the pharmaceutically acceptable salts thereof wherein Q, X, Y, Z, and R₁, R₉, and R₁₂-R₁₉ are defined herein. These compounds are selective modulators of MCH 1 receptors that are, therefore, useful in the treatment of a variety of metabolic, feeding, and sexual disorders. Methods of treatment of such disorders and well as packaged pharmaceutical compositions are also disclosed.

WO 02/0433 A2

Melanin Concentrating Hormone Receptor Ligands

Background of the Invention

5 This application claims priority from U.S. Provisional Application S.N. 60/216,081, filed July 6, 2000.

Field of the invention

10 This invention relates to phenylcycloalkylmethylamino and phenylalkenylamino derivatives, including 1-phenyl-2-aminomethylcyclopropanes, that are modulators of melanin concentrating hormone type 1 (MCH 1) receptors. This invention also relates to pharmaceutical compositions comprising such compounds.

Description of the Related Art

15 Melanin concentrating hormone, or MCH, is a cyclic 19 amino acid neuropeptide that is produced within the hypothalamus of many vertebrate species including man. I.C.V. injection of MCH into the lateral ventricle of the hypothalamus has been shown to increase caloric consumption in rats over similarly treated control animals. Furthermore, rats having the *ob/ob* genotype exhibit a 50-80% increase in MCH mRNA expression as compared to leaner *ob/+* genotype mice. MCH knockout mice are leaner than their MCH-producing
20 siblings due to hypophagia and an increased metabolic rate. Thus, MCH is thought to be an important regulator of feeding behavior and body weight.

25 The MCH 1 receptor was originally obtained from human cDNA and genomic libraries and characterized as a 402 amino acid G-coupled protein receptor having substantial sequence identity to the somatostatin receptors. This receptor was named the SLC-1 receptor. A rat orthologue of the MCH 1 receptor was isolated from a rat brain cDNA library by Lakaye, et al. (BBA (1998) 1401: 216-220) and found to encode a 353 amino acid protein having seven transmembrane alpha helices and three consensus *N*-glycosylation sites. The rat MCH 1 receptor reported by Lakaye also disclosed was homologous to the human MCH 1 receptor disclosed earlier except for the removal of a 5' intron. Accordingly, Lakaye, et al.,
30 deduced the "corrected" amino acid sequence of the N-terminus of MCH 1 receptor is found within a sequence deposited for a 128 kb fragment of human chromosome 22 encompassing the earlier disclosed MCH 1 receptor gene (Genbank accession number: Z86090).

The earlier reported 402 amino acid MCH 1 receptor protein does not interact with MCH. Thus, the 353 amino acid receptor first reported by Lakaye, is now considered to be the correct full-length sequence for the human MCH 1 receptor.

Immunohistochemistry studies of rat brain sections indicate that the MCH 1 receptor is
5 widely expressed in the brain. MCH 1 receptor expression was found in the olfactory tubercle, cerebral cortex, substantia nigra, basal forebrain CA1, CA2, and CA3 field of the hippocampus, amygdala, and in nuclei in the hypothalamus, thalamus, midbrain and hindbrain. Strong signals have been observed in the ventromedial and dorsomedial nuclei of the hypothalamus, two areas of the brain known to be involved in feeding behavior.

10 Upon binding MCH, MCH 1 receptors expressed in HEK 293 cell mediate a dose dependent release of intracellular calcium. Cells expressing MCH receptors have also been shown to exhibit a pertussis toxin sensitive dose-dependent inhibition of forskolin-elevated cyclic AMP, indicating that the receptor couples to a $G_{i/o}$ G-protein alpha subunit.

Because MCH has been shown to be an important regulator of food intake and energy
15 balance, ligands capable of modulating the activity of the MCH 1 receptor are highly desirable for the treatment of eating disorders and metabolic disorders. Orally available, small molecule, non-peptide antagonists of the MCH 1 receptor are particularly sought for the treatment of obesity.

20

SUMMARY OF THE INVENTION

The invention provides novel compounds, particularly phenylcycloalkylmethylamino and phenylalkenylamino compounds, including 1-phenyl-2-aminomethylcyclopropanes, that are small molecule MCH receptor ligands, especially MCH 1 receptor ligands, that are non-peptide and amino acid free, which compounds exhibit a K_i at the MCH receptor of less than 1 micromolar. Preferred MCH 1 receptors are mammalian receptors, including human and monkey MCH receptors and may either be cloned, recombinantly expressed receptors or naturally expressed receptors.

In certain embodiments these compounds also possess one or more, and preferably two or more, three or more, or all of the following properties in that they are: 1) multi-aryl in structure (having a plurality of un-fused or fused aryl groups), 2) orally available *in vivo* (such that a sub-lethal or pharmaceutically acceptable oral dose can provide a detectable *in vivo* effect such as a reduction of appetite), 3) capable of inhibiting the binding of MCH to the MCH receptor at nanomolar concentrations or 4) capable of inhibiting the binding of MCH to the MCH receptor at sub-nanomolar concentrations.

The invention also provides novel compounds of Formula I, shown below, that bind specifically, and preferably with high affinity, to MCH receptors.

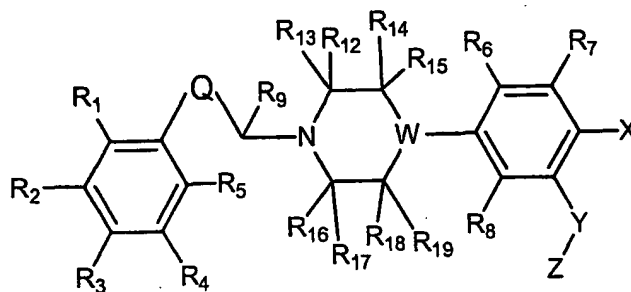
The invention also provides pharmaceutical compositions comprising compounds of Formula I together with at least one pharmaceutically acceptable carrier. The compounds are particularly useful in the treatment of metabolic, feeding, and sexual disorders. The invention further comprises a method of treating a patient in need of such treatment with a sufficient concentration of a compound of the invention. A preferred concentration is one sufficient to inhibit the binding of MCH to MCH 1 receptors *in vitro*. Treatment of humans, domesticated companion animals (pets) or livestock animals suffering such conditions with an effective amount of a compound of the invention is contemplated by the invention.

Also included in the invention are methods of treating eating disorders, particularly obesity and bulimia nervosa, comprising administering to a patient in need of such treatment a MCH 1 receptor modulator together with leptin, a leptin receptor agonist, or a melanocortin receptor 4 (MC4) agonist.

In a separate aspect, the invention provides methods of using compounds of this invention as positive controls in assays for receptor activity and using appropriately labeled compounds of the invention as probes for the localization of receptors, particularly MCH receptors, in tissue sections.

The invention provides compounds and compositions that are useful as inhibitors of MCH binding to MCH 1 receptor, and as inhibitors of MCH mediated signal transduction (e.g., they may be used as standards in assays of MCH binding and MCH-mediated signal transduction). The invention additionally comprises methods of inhibiting MCH binding to MCH receptors *in vivo*, preferably MCH 1 receptors present in the hypothalamus.

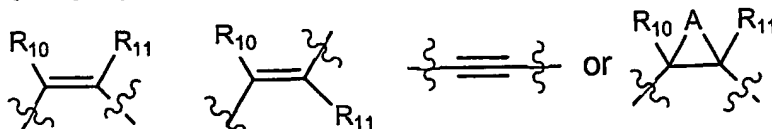
Accordingly, a broad embodiment of the invention is directed to a compounds and pharmaceutically acceptable salts of Formula I:



I

wherein:

Q is a group of the Formula:



wherein

- 15 A is C₁-C₅ alkylene optionally mono-, di, or trisubstituted with substituents independently chosen from C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, halo(C₁-C₃)alkyl, halo(C₁-C₃)alkoxy, hydroxy, amino, and mono- or di(C₁-C₃)alkylamino;
- R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ are the same or different and represent hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio,
- 20 hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -SO₂NH₂, mono or dialkylsulfonamido, -C(O)NH₂, or mono or di(C₁-C₆)alkylcarboxamido;
- R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ independently represent hydrogen or C₁-C₆ alkyl;
- 25 W is nitrogen or C-R_a where R_a represents hydrogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl or cyano;

X represents halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkylamino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -CONH₂, mono- or di(C₁-C₆)alkylcarboxamido, -SO₂NH₂, mono or di(C₁-C₆)alkylsulfonamido; or

- 5 X represents phenyl which may be optionally substituted by up to five substituents, which may be the same or different and are selected from the group consisting of hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -CONH₂, mono- or di-(C₁-C₆)alkylcarboxamido, -SO₂NH₂, and mono or di(C₁-C₆)alkylsulfonamido;
- 10

Y is oxygen, sulfur, -S(O)-, or -SO₂-; and

Z is C₁-C₆ alkyl or mono, di or trifluoromethyl.

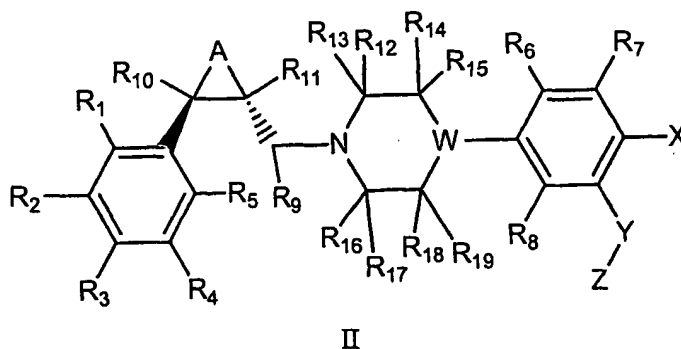
The invention also provides intermediates and methods useful for preparing the compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention particularly includes compounds and salts of Formula I wherein Q is a ring and A is methylene optionally substituted with C₁-C₂ alkyl.

5 The invention is also specifically directed to compounds and salts of Formula I wherein W is nitrogen or CH and A is methylene. Preferred compounds and salts of this class are those wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen. Other preferred compounds and salts of this class are those wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen, X is halogen; Y is oxygen; and Z is C₁-C₆ alkyl. Also
 10 preferred are compounds and salts of Formula I wherein W is nitrogen or CH and A is methylene, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy; X is hydrogen, halogen, or phenyl, or most preferably X is halogen; Y is oxygen; and Z is C₁-C₆ alkyl.

15 Particularly provided by the invention are compounds of Formula II



and the pharmaceutically acceptable salts thereof; wherein

A is methylene optionally substituted with C₁-C₂ alkyl, and R₁-R₁₉, W, X, Y, and Z are as
 20 defined for Formula I.

Preferred compounds and salts of Formula II are those wherein W is nitrogen or CH.

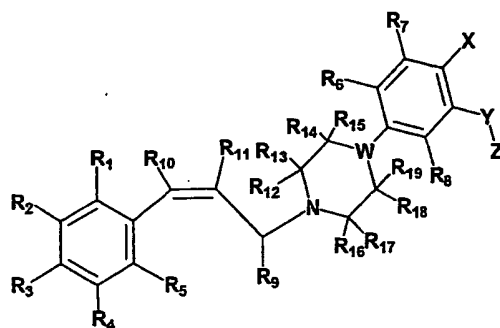
Other preferred compounds and salts of Formula II are those wherein W is nitrogen or CH and R₁₀, R₁₁, R₁₂, R₁₃, R₁₅, R₁₇, R₁₈, and R₁₉ are hydrogen.

Also preferred are compounds and salts of Formula II wherein W is nitrogen or CH,
 25 R₁₀, R₁₁, R₁₂, R₁₃, R₁₅, R₁₇, R₁₈, and R₁₉ are hydrogen, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ independently represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy; R₁₄ and R₁₆ are the same or different and are either hydrogen or methyl; X is hydrogen, halogen, or phenyl; Y is oxygen; and Z is C₁-C₆ alkyl.

Particularly preferred compounds and salts of Formula II are those wherein W is nitrogen or CH, R₁, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen,

R₂, R₃, R₄, and R₅ are independently hydrogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, or halogen; X is
 5 halogen; Y is oxygen; and Z is C₁-C₆ alkyl.

The invention further provides compounds of Formula III



III

10 and the pharmaceutically acceptable salts thereof, wherein R₁-R₁₉, W, X, Y, and Z are as defined for Formula I.

Preferred compounds and salts of Formula III are those wherein R₁₃, R₁₅, R₁₇, R₁₉ are hydrogen; and R₁₀, R₁₁, R₁₂, R₁₄, R₁₆, and R₁₈ independently represent hydrogen or methyl, or
 15 more preferably hydrogen.

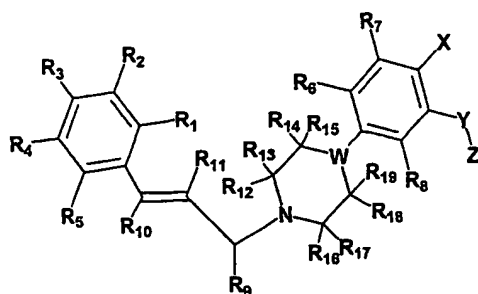
Also preferred are compounds and salts of Formula III, wherein R₁₀-R₁₉ are hydrogen, and W is N or CH.

More preferred compounds and salts of Formula III are those wherein R₁₀-R₁₉ are hydrogen, W is N or CH; R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ independently represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy; X is hydrogen or
 20 halogen; Y is oxygen; and Z is C₁-C₆ alkyl.

Particularly preferred compounds and salts of Formula III are those wherein R₁₀-R₁₉ are hydrogen, W is N or CH, R₁, R₂, R₃, R₄ independently represent hydrogen, halogen, C₁-C₂alkyl, or C₁-C₂ alkoxy; R₅, R₆, R₇, and R₈ are hydrogen; X is halogen; Y is oxygen; and Z
 25 is C₁-C₆ alkyl.

Another embodiment of the invention is directed to compounds and salts of Formula

IV



IV

and the pharmaceutically acceptable salts thereof, wherein R_1 - R_{19} , W, X, Y, and Z are as defined for Formula I.

5

Preferred compounds and salts of Formula IV are those wherein R_{13} , R_{15} , R_{17} , R_{19} , are hydrogen; and R_{10} , R_{11} , R_{12} , R_{14} , R_{16} , and R_{18} independently represent hydrogen or methyl, or more preferably hydrogen.

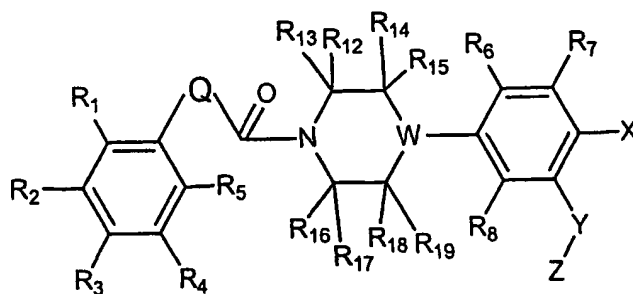
Also preferred are compounds and salts of Formula IV, wherein R_{10} - R_{19} are hydrogen, and W is N or CH.

More preferred compounds and salts of Formula IV are those wherein R_{10} - R_{19} are hydrogen, W is N or CH; R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , and R_8 independently represent hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, trifluoromethyl, or trifluoromethoxy; X is hydrogen or halogen; Y is oxygen; and Z is C_1 - C_6 alkyl.

Particularly preferred compounds and salts of Formula IV are those wherein R_{10} - R_{19} are hydrogen, W is N or CH, R_1 , R_2 , R_3 , R_4 independently represent hydrogen, halogen, C_1 - C_2 alkyl, or C_1 - C_2 alkoxy; R_5 , R_6 , R_7 , and R_8 are hydrogen; X is halogen; Y is oxygen; and Z is C_1 - C_6 alkyl.

20

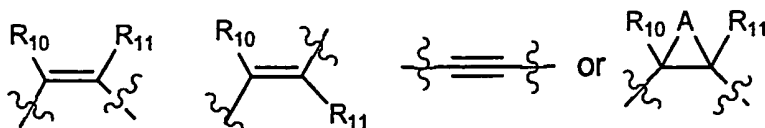
The invention also provides compounds of Formula V



V

or a pharmaceutically acceptable salt thereof wherein:

Q is a group of the Formula:



wherein:

A is C₁-C₅ alkylene optionally mono-, di, or trisubstituted with substituents independently
 5 chosen from C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, halo(C₁-C₃)alkyl, halo(C₁-C₃)alkoxy, hydroxy, amino, and mono- or di(C₁-C₃)alkylamino;

R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ are the same or different and represent hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy,
 10 C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -SO₂NH₂, mono or dialkylsulfonamido, -C(O)NH₂, or mono or di(C₁-C₆)alkylcarboxamido;

R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ independently represent hydrogen or C₁-C₆ alkyl;

W is nitrogen or C-R_a where R_a represents hydrogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl or
 15 cyano;

X represents halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkylamino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -CONH₂, mono- or di(C₁-C₆)alkylcarboxamido, -SO₂NH₂, mono or di(C₁-C₆)alkylsulfonamido; or

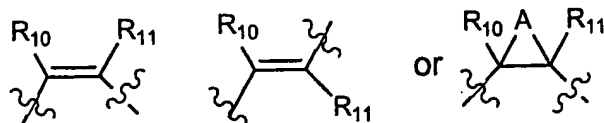
20 X represents phenyl which may be optionally substituted by up to five substituents, which may be the same or different and are selected from the group consisting of hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -CONH₂, mono- or di-(C₁-C₆)alkylcarboxamido, -SO₂NH₂, and mono or di(C₁-C₆)alkylsulfonamido;

Y is oxygen, sulfur, -S(O)-, or -SO₂-; and

Z is C₁-C₆ alkyl or mono, di or trifluoromethyl.

Compounds of Formula V are intermediates, useful in preparing compounds MCH 1
 30 receptor ligands.

Preferred compounds of Formula V are those wherein Q is a group the formula



where A is methylene optionally substituted with C₁-C₂ alkyl or A is a single bond. Such compounds will be referred to as compounds of Formula VA.

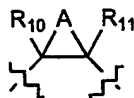
5 The invention is particularly directed to compounds of Formula VA wherein W is nitrogen or CH.

More preferred compounds of Formula VA are those wherein W is nitrogen or CH, and R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen.

Other preferred compounds of Formula VA are those wherein W is nitrogen or CH,
10 R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen, X is halogen; Y is oxygen; and Z is C₁-C₆ alkyl.

Especially preferred compounds of Formula VA are those wherein W is nitrogen or CH, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen, R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆
15 alkoxy, trifluoromethyl, or trifluoromethoxy, X is halogen; Y is oxygen; and Z is C₁-C₆ alkyl.

Particularly preferred compounds of Formula V include those where Q is a group of the formula:



where A is methylene optionally substituted with C₁-C₂ alkyl. These compounds are
20 hereinafter referred to as compounds of Formula VI-A. Specific compounds of Formula VI-A include those where A is methylene and R₁₀ and R₁₁ are methyl or, preferably, hydrogen.

Specific compounds of VA include those wherein W is nitrogen or CH. Preferred compounds of V and VA include those wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen.

25 Other specific compounds of VA include those wherein: X is halogen; Y is oxygen; and Z is C₁-C₆ alkyl.

Still other specific compounds of VA include those where R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ are the same or different and represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

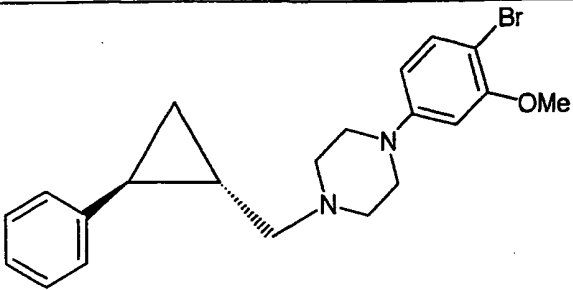
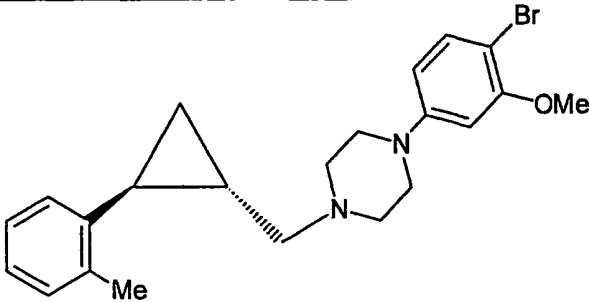
30 X is halogen;

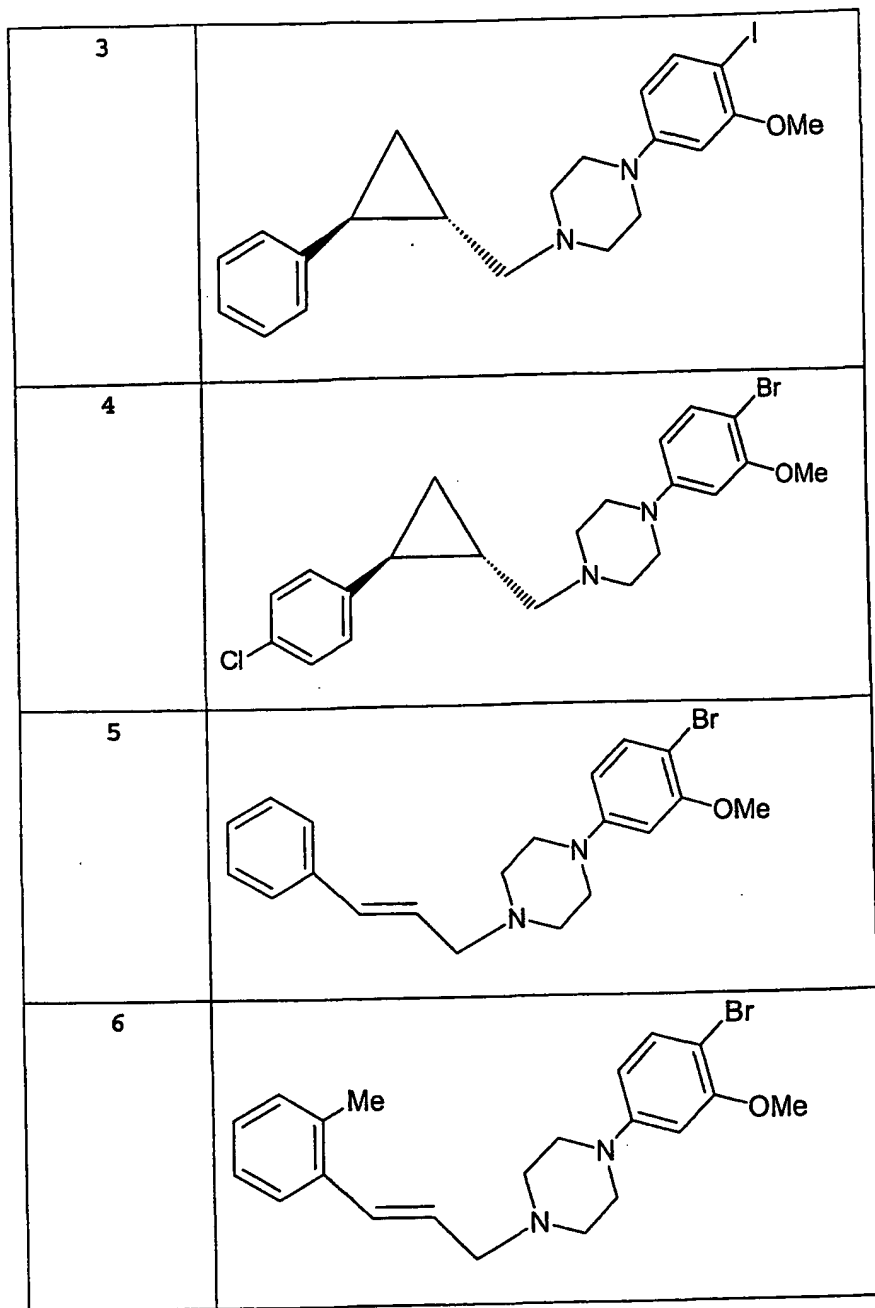
Y is oxygen; and

Z is C₁-C₆ alkyl.

- 5 Preferably not more than 5, and more preferably not more than 3, cyano or nitro groups are present in compounds of Formula I – Formula VA. Preferably not more than 2 of R₁, R₂, R₃, R₄, R₅ are non-hydrogen substituents. Preferably not more than 5 and more preferably not more than 3 of R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are non-hydrogen substituents.

Representative compounds of Formula I are shown in Table 1.

Table 1	
Compound number	Chemical Structure
1	
2	



In certain situations, the compounds of this invention may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for example, racemates or optically active forms. In these situations, the single enantiomers, i.e., optically active forms, can be obtained by asymmetric synthesis or by resolution of the racemates. Asymmetric synthesis of compounds of the invention may be performed using the methods illustrated in Example 1, below. For

compounds having an alpha-methyl benzyl group (R_3 is methyl, R_4 is hydrogen) the R enantiomer is preferred. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral HPLC column.

5 Representative compounds of the invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable acid addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically
10 acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds.

Non-toxic pharmaceutical salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic,
15 citric, tartaric, maleic, hydroiodic, alkanolic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be
20 employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

Where a compound exists in various tautomeric forms, the invention is not limited to any one of the specific tautomers. The invention includes all tautomeric forms of a compound.

This invention relates to compounds that bind with high affinity to the melanin
25 concentrating hormone receptors, including human melanin concentrating hormone receptors. This invention also includes such compounds that bind with high selectivity to the melanin concentrating hormone receptors, including human and monkey melanin concentrating hormone receptors. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds of Formula I with the melanin concentrating hormone
30 receptor results in the pharmaceutical utility of these compounds.

The invention further comprises methods of treating patients in need of such treatment with an amount of a compound of the invention sufficient to alter the symptoms of a disorder.

The diseases and/ or disorders that can also be treated using compounds and compositions according to the invention include, but are not limited to, eating disorders,

sexual disorders, obesity, bulimia, anorexia, diabetes, heart disease, stroke, anorgasmia, or psychogenic impotence.

The invention also provides pharmaceutical compositions comprising at least one compound of the invention together with at least one pharmaceutically acceptable carrier or excipient. Such pharmaceutical compositions include packaged pharmaceutical compositions for treating disorders responsive to melanin concentrating hormone receptor modulation, e.g., treatment of eating disorders such as obesity or bulimia or treatment of sexual disorders such as anorgasmic or psychogenic impotence. The packaged pharmaceutical compositions include a container holding a therapeutically effective amount of at least one melanin concentrating hormone receptor modulator as described supra and instructions (e.g., labeling) indicating that the contained composition is to be used for treating a disorder responsive to melanin concentrating hormone receptor modulation in the patient.

The invention also pertains to methods of inhibiting the binding of melanin concentrating hormone to melanin concentrating hormone receptors which methods involve contacting a compound of the invention with cells expressing melanin concentrating hormone receptors, wherein the compound is present at a concentration sufficient to inhibit melanin concentrating hormone binding to melanin concentrating hormone receptors *in vitro*. This method includes inhibiting the binding of melanin concentrating hormone to melanin concentrating hormone receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to inhibit the binding of melanin concentrating hormone to melanin concentrating hormone receptors *in vitro*. The amount of a compound that would be sufficient to inhibit the binding of melanin concentrating hormone to the melanin concentrating hormone receptor *in vitro* may be readily determined via a melanin concentrating hormone receptor binding assay, such as the assay described in Example 5. The membranes, comprising melanin concentrating hormone receptors, used to determine *in vitro* binding may be obtained from a variety of sources, for example from preparations of HEK 293 cells expressing cloned human or cloned monkey melanin concentrating hormone receptors, especially HEK 293 cells expressing such receptors.

The invention also pertains to methods for altering the signal-transducing activity of MCH receptors, particularly the MCH receptor-mediated release of intracellular calcium, said method comprising exposing cells expressing such receptors to an effective amount of a compound of the invention. This method includes altering the signal-transducing activity of MCH receptors *in vivo*, e.g., in a patient given an amount of a compound of Formula I that would be sufficient to alter the signal-transducing activity of MCH receptors *in vitro*. The

amount of a compound that would be sufficient to alter the signal-transducing activity of MCH receptors may be determined via a MCH receptor signal transduction assay, such as the calcium mobilization assay described in Example 6.

5 The melanin concentrating hormone receptor ligands provided by this invention and labeled derivatives thereof are also useful as standards and reagents in determining the ability of a potential pharmaceutical to bind to the melanin concentrating hormone receptor.

Labeled derivatives the melanin concentrating hormone receptor ligands provided by this invention are also useful as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT).

10 Preferred compounds of the invention do not exhibit fungicidal activity. Such a lack of fungicidal activity may be demonstrated by no more than a 40% reduction of colony size (when treated with the compound at 100 p.p.m. and compared to untreated controls) of *Aspergillus nidulans* strain R153 when grown for 48 hours at 32°C on solid MAG medium. Optionally, BENOMYL, 100 p.p.m., may be used as a positive control. MAG medium is 2%
15 malt extract, 0.2% peptone, 1% glucose and trace elements, pH 6.5. Trace elements as a 5000-fold concentrate consist of 10 g/l EDTA, 4.4 g/l ZnSO₄·7H₂O, 1.01 g/l MnCl₂·4H₂O, 0.32 g/l CoCl₂·6H₂O, 0.315 g/l CuSO₄·5H₂O, 0.22 g/l (NH₄)₆Mo₇O₂₄·H₂O, 1.47 g/l CaCl₂·2H₂O and 1.0 g/l FeSO₄·7H₂O. Medium is made solid by the addition of 1.5% agar.

Alternatively, such a lack of fungicidal activity may be demonstrated by an infection
20 frequency of 60-100% (as compared to untreated plants) for each of *Puccinia recondita* (leaf rust) on wheat, *Erysiphe graminis* (powdery mildew) on barley, *Venturia inaequalis* (scab, black spot) on apple plants, and *Cercospora arachidicola* (early leafspot) on peanut.

The technique employed to determine fungicidal activity is as follows. The plants are grown in John Innes Potting Compost (No. 1, or Seed, as appropriate) in 4 cm diameter mini-
25 pots. A layer of fine sand is placed at the bottom of the pot to facilitate uptake of test compound by the roots.

The test compounds are formulated, e.g., by bead-milling with aqueous Dispersol T or as a solution in acetone/ethanol which is diluted to the required concentration immediately before use. 100 p.p.m. a.i. suspensions are sprayed on to the foilage and applied to the roots of
30 the same plant via the soil. (Sprays are applied to maximum retention, and root drenches to a final concentration equivalent to approximately 40 ppm a.i./dry soil). Tween 20, to give a final concentration of 0.1%, is added when the sprays are applied to the cereals.

For most of the tests, the test compound is applied to the soil (roots) and to the foliage (by spraying) one or two days before the plant is inoculated with the diseases. An

exception is the test on *Erysiphe graminis*, in which the plants are inoculated 24 hours before treatment. After inoculation, the plants are put into an appropriate environment to allow infection to take place and then incubated until the disease is ready for assessment. The period between inoculation and assessment typically varies from 4 to 14 days according to the disease and environment.

Chemical Description and Terminology

The compounds of the invention have asymmetric centers; this invention includes all of the optical isomers and mixtures thereof.

Compounds of the invention with carbon-carbon double bonds occur in Z- and E-forms; all isomeric forms of the compounds are included in the invention.

When any variable occurs more than one time in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

By "C₁-C₆ alkyl" or in the invention is meant straight or branched chain alkyl groups or cycloalkyl groups having 1-6 carbon atoms, such as, for example, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl. Preferred C₁-C₆ alkyl groups are methyl, ethyl, propyl, butyl, cyclopropyl, cyclopropylmethyl, cyclohexyl, cycloheptyl, norbornyl, and the like. Particularly preferred alkyl groups are methyl and ethyl.

By "C₁-C₆ alkoxy" in the invention is meant an alkyl group of indicated number of carbon atoms attached through an oxygen bridge such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Preferred alkoxy groups herein are C₁-C₄ alkoxy groups. Particularly preferred alkoxy groups are ethoxy and methoxy.

The term "halogen" includes fluorine, chlorine, bromine, and iodine. Where X is halogen in Formula I- Formula V, bromine is particularly preferred.

"Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen atoms. Examples of haloalkyl include, but are not limited to, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-chloromethyl, mono-, di-, tri-, tetra-, or penta-fluoroethyl, and mono-, di-, tri-, tetra-, or penta-chloroethyl. Typical haloalkyl groups are trifluoromethyl and

difluoromethyl. Preferably not more than 5, and more preferably not more than 3 haloalkyl groups, are present in compounds of the invention.

"Haloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge.

5 Non-toxic "pharmaceutically acceptable salts" include, but are not limited to salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrite or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, 2-hydroxyethylsulfonate, salicylate and stearate. Similarly, pharmaceutically acceptable cations include, but are not
10 limited to sodium, potassium, calcium, aluminum, lithium and ammonium. The invention also encompasses the prodrugs of the compounds of Formula I.

Pharmaceutical preparations

Those skilled in the art will recognize various synthetic methodologies that may be
15 employed to prepare non-toxic pharmaceutically acceptable prodrugs of the compounds encompassed by Formula I. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable solvents that may be used to prepare solvates of the compounds of the invention, such as water, ethanol, mineral oil, vegetable oil, and dimethylsulfoxide.

The compounds of general Formula I may be administered orally, topically,
20 parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. Oral administration in the form of a pill, capsule, elixir, syrup, lozenge, troche, or the like is particularly preferred. The term parenteral as used herein includes subcutaneous injections, intradermal, intravascular (e.g., intravenous), intramuscular, spinal, intrathecal injection or
25 like injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of
30 general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may

contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These
5 excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and
10 absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium
15 phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose,
20 sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters
25 derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more
30 sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and

flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monoleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monoleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general Formula I may also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

5 For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

10 Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per human patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain
15 between from about 1 mg to about 500 mg of an active ingredient.

Frequency of dosage may also vary depending on the compound used and the particular disease treated. However, for treatment of most disorders, a dosage regimen of 4 times daily or less is preferred. For the treatment of eating disorders, including obesity, a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of impotence
20 a single dose that rapidly reaches effective concentrations is desirable.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular
25 disease undergoing therapy.

Preferred compounds of the invention will have desirable pharmacological properties. Such properties include, but are not limited to oral bioavailability, low toxicity, low serum protein binding and desirable *in vitro* and *in vivo* half-lives. Penetration of the blood brain barrier for compounds used to treat CNS disorders is necessary, while low brain levels of
30 compounds used to treat peripheral disorders are often preferred.

Assays may be used to predict these desirable pharmacological properties. Assays used to predict bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Toxicity to cultured hepatocytes may be used to predict compound toxicity. Penetration of the blood brain barrier of a compound in humans may be

predicted from the brain levels of the compound in laboratory animals given the compound intravenously.

Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996) volume 677, pages 1-27).

Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described by Kuhnz and Gieschen (Drug Metabolism and Disposition, (1998) volume 26, pages 1120-1127).

Compounds of Formula I exhibit good activity in standard *in vitro* MCH receptor binding assays and/ or calcium mobilization assays, specifically in the assays as specified in Examples 5 and 6, which follow. References herein to "standard *in vitro* receptor binding assay" are intended to refer to that protocol as defined in Example 5 which follows. References herein to "standard MCH 1 receptor calcium mobilization assay" are intended to refer to that protocol as defined in Example 6 which follows. Generally, preferred compounds of Formula I have an K_i of about 1 micromolar or less, still more preferably a K_i of about 100 nanomolar or less even more preferably a K_i of about 10 nanomolar or less or even 1 nanomolar or less in such a defined standard *in vitro* MCH 1 receptor binding assay and exemplified by Example 5. Generally preferred compounds of Formula I are MCH 1 receptor antagonists and exhibit EC_{50} values of about 4 micromolar or less, more preferably 1 micromolar or less, still more preferably EC_{50} values of about 100 nanomolar or less even more preferably an EC_{50} value of about 10 nanomolar or less or even 1 nanomolar or less in such a defined standard *in vitro* MCH 1 receptor mediated calcium mobilization assay as exemplified by Example 6 which follows.

Preferred compounds of Formula I do not interact with dopamine receptors, particularly human dopamine D2 and D4 receptors. Dopamine receptor binding assays may be preformed using the methods described in Example 9 which follows. Preferred compounds of Formula I exhibit K_i values greater than 1 micromolar in standard assays of dopamine receptor binding assays such as the dopamine D2 and D4 receptor binding assays described in Example 9.

EXAMPLES

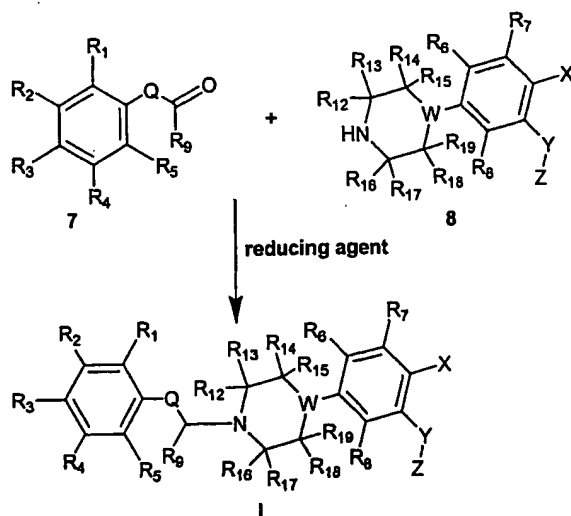
Preparation of compounds

The compounds of the invention can be prepared essentially according to the synthetic procedure shown in Scheme 1. As shown, a 2-phenylacylcycloalkyl compound of general structure 7 may be condensed with a 4-arylpiperazine or piperidine of general structure 8 in the presence of a reducing agent to provide a compound of general Formula I. The reducing agent may be sodium borohydride, sodium triacetoxy borohydride, lithium aluminum hydride, alane or the like. Alternatively, an acid chloride or an acid can be coupled with the piperazine to generate an amide, which can in turn be reduced to yield the desired compound of Formula I.

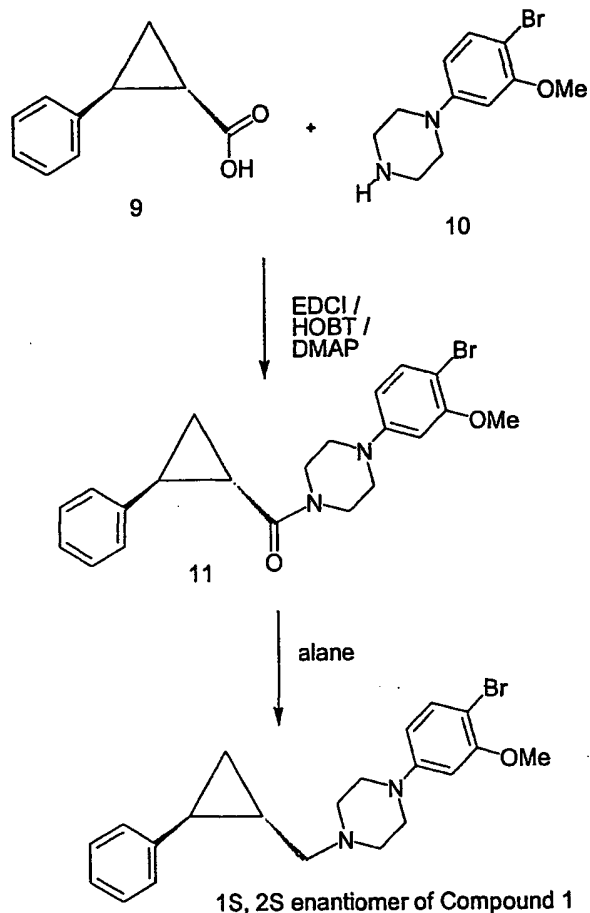
The preparation of a specific compound of this invention (the 1S,2S enantiomer of Compound 1) is described graphically in Scheme 2 and the synthetic steps used are presented within Example 1. Within Scheme 2, 1S,2S 2-phenylcyclopropanecarboxylic acid (9) was condensed with 1-(4-bromo-3-methoxyphenyl)piperazine (10) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), dimethylaminopyridine (DMAP) and 1-hydroxybenzotriazole (HOBT). The resulting amide 11 was reduced to the desired amine by reduction with alane in tetrahydrofuran.

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the invention, as demonstrated by the following examples. Unless otherwise specified all reagents and solvent are of standard commercial grade and are used without further purification.

Scheme 1



Scheme 2
Preparation of 1*S*,2*S* Enantiomer of Compound I



5

Example 1.**Preparation of (1*S*, 2*S*)-1-(4-bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl)methylpiperazine.**

10 Compound numbers 9-11 in the following example represent compounds shown in Scheme 2.

1-(4-Bromo-3-methoxyphenyl)piperazine (10)

A solution of 1-(3-methoxyphenyl)piperazine dihydrobromide (3.5 g, 10 mmol) is dissolved in DMSO (30 mL) and heated at 65 °C for 4h in a flask which is open to the atmosphere. After cooling, the mixture is poured into a separatory funnel containing 100 mL

15

of 1 N sodium hydroxide solution and extracted with ethyl ether (3 X 100 mL). The organic extracts are dried (Na₂SO₄), filtered, and concentrated to provide 1-(4-bromo-3-methoxyphenyl)piperazine as a solid. ¹H NMR (400 MHz, CDCl₃) 7.34-7.36 (d, J=2.2 Hz, 1H), 6.47 (s, 1H), 6.38-6.41 (d, J = 2.8 Hz, 1H), 3.87 (s, 3H, OMe), 3.11-3.13 (m, 4H), 3.01-3.03 (m, 4H)

(1S,2S)-1-(4-bromo-3-methoxyphenyl)-4-(trans-2-phenylcyclopropyl) carbonylpiperazine (11).

EDCI (0.42g, 2.2 mmol), DMAP (0.27 g, 2.2 mmol) and HOBT (0.23 g, 2.2 mmol) are added to a solution of acid 9 (0.34 g, 2.1 mmol) and piperazine 10 (0.54 g, 2.0 mmol) in chloroform (15 mL) and the resulting solution allowed to stir overnight. The solution is washed with water (10 mL), saturated NaHCO₃ solution, (10 mL), brine (10 mL) and dried over magnesium sulfate. After filtration the solution is concentrated and the resulting oil purified by column chromatography eluting with 2% methanol in chloroform to provide the desired amide 11 as a white sticky solid. ¹H NMR (400 MHz, CDCl₃) δ 7.1-7.5 (m, 6H), 6.50 (s, 1H), 6.40 (d, J = 7 Hz, 1H), 3.89 (s, 3H, OMe), 3.8 (bm, 4H), 3.2 (bm, 4H), 2.5 (m, 1H), 1.98 (m, 1H), 1.70 (m, 1H), 1.35 (m, 1H), LCMS (CI) 416 (M+1).

(1S, 2S)-1-(4-bromo-3-methoxyphenyl)-4-(trans-2- phenylcyclopropyl) methylpiperazine (Compound 1, Table 1)

A solution of alane triethylamine complex (3.13 mL, 1.57 mmol) is added to a solution of amide 11 (0.65 g, 1.57 mmol) in THF (10 mL) at 0 °C. After 45 min, the reaction is quenched with water and extracted with ether. The organic extracts are dried (MgSO₄), filtered, and concentrated to a colorless oil which is purified by column chromatography eluting with 5% MeOH/chloroform to provide the desired compound 1 as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, J = 7 Hz, 1H), 7.1-7.35 (m, 5H), 6.45 (d, J = 1 Hz, 1H), 6.40 dd, J = 7, 1 Hz, 1H), 3.88 (s, 3H, OMe), 3.2 (m, 4H), 2.7 (m, 4H), 2.63 (m, 1H), 2.40 (dd, J = 12, 5 Hz, 1H), 1.70 (m, 1H), 1.25 (m, 1H), 0.85-1.0 (m, 2H).

Example 2

The following compounds are prepared essentially according to the procedures described with respect to Schemes 1 and 2 and further set forth in Example 1. Variations

suitable for preparing the following compounds will be readily apparent to those skilled in the art of organic synthesis:

- a) 1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine
- 5 b) 1*R*, 2*R*-1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine
- c) 1-(4-Iodo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine
- d) 1-(4-Chloro-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine
- e) 1-(4-Phenyl-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine
- f) 1-(4-Bromo-3-methoxyphenyl)-4-[*trans*-2-(3-methoxyphenyl)cyclopropyl]
- 10 methylpiperazine
- g) 1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-[4-chlorophenyl] cyclopropyl) methylpiperazine
(compound 4)
- h) 1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-[2-methylphenyl] cyclopropyl)methylpiperazine
(compound 2)
- 15 i) 1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-[4-methoxyphenyl]
cyclopropyl)methylpiperazine
- j) 1-(4-Bromo-3-methoxyphenyl)-4-([3-phenyl]propen-2-yl)piperazine (Compound 5)
- k) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{2-methylphenyl}]propen-2-yl)piperazine
(compound 6)
- 20 l) 1-(3-Methoxyphenyl)-4-([3-phenyl]propen-2-yl)piperazine
- m) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{3-methylphenyl}]propen-2-yl)piperazine
- n) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{2-methoxyphenyl}]propen-2-yl)piperazine
- o) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{3-chlorophenyl}]propen-2-yl)piperazine
- p) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{3-ethoxyphenyl}]propen-2-yl)piperazine
- 25 q) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{2,3-dimethoxyphenyl}]propen-2-yl)piperazine
- r) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{3,4-dimethoxyphenyl}]propen-2-yl)piperazine
- s) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{2,5-dimethoxyphenyl}]propen-2-yl)piperazine
- t) 1-(4-Bromo-3-methoxyphenyl)-4-([3-{2,4-dimethoxyphenyl}]propen-2-yl)piperazine
- u) 1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine
- 30 v) 1-(4-Iodo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine
- w) 1-(4-Chloro-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine
- x) 1-(4-Methyl-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine
- y) 1-(4-Trifluormethyl-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine
- z) 1-(4-Bromo-3-ethoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine.

Example 3.**Cells expressing MCH 1 Receptors**

Cells or preparations of cells recombinantly expressing human MCH 1 receptors,
5 monkey MCH 1 receptors, or chimeric human MCH 1/human Beta 2 Adrenergic receptors
may be used in the radioligand binding assay and Calcium Mobilization assay which follows.
The preparation of expression vectors for such MCH 1 Receptors has been described
previously, e.g. in U.S. Provisional Application No. 60/216,081, filed July 6, 2000 and U.S.
Provisional Application 60/284,835, filed April 19, 2001, pages 19-20 and the sequence
10 listing, both of which application are hereby incorporated by reference for their teachings
regarding the cloning and expression of MCH 1 receptors.

Preparation of HEK 293 cells expressing the monkey MCH receptor

HEK 293 cells are stably transfected via standard calcium phosphate precipitation
procedures with a Cynomolgus macaque monkey MCH expression vector described
15 previously or other MCH 1 receptor expression vector.

Cells are grown to confluency at 37 C, 5% CO₂, approximately 48-72 hours, in
DMEM high glucose culture medium (catalog #10-017-CV, MEDiatech, Herndon, VA)
supplemented with 10% fetal bovine serum, 25 mM HEPES, and 500 ug/ml G418. The cells
are pelleted by gentle centrifugation. Cell pellets are washed twice with cold PBS, harvested
20 in cold PBS containing 5 mM EDTA, and stored at -80 C.

Preparation of CHO cells expressing the monkey MCH receptor

CHO (Chinese Hamster Ovary) cells are transfected via standard calcium phosphate
precipitation procedures with an MCH 1 receptor expression vector.

Cells are grown to confluency at 37 C, 5% CO₂, approximately 48-72 hours, in Ham's
25 F12 culture medium (catalog #10-080-CV, MEDiatech, Herndon, VA) supplemented with
10% fetal bovine serum, 25 mM HEPES, and 500 ug/ml (active) G418. The cells are pelleted
by gentle centrifugation. Cell pellets are washed twice with cold PBS, harvested in cold PBS
containing 5 mM EDTA, and stored at -80 °C.

Example 4.**Purified Membranes**

HEK 293 cell pellets stored frozen at -80 °C are thawed by addition of wash buffer
(25 mM Hepes with 1.0mM CaCl₂, 5.0mM MgCl₂, 120mM NaCl, PH7.4) and homogenized
for 30 seconds using a BRINKMAN POLYTRON, setting 5. Cells are centrifuged for 10

minutes at 48,000 x g. The supernatant is discarded and the pellet is resuspended in fresh wash buffer, and homogenized again. The protein concentration of the resulting membrane preparation is measured using the Bradford protein assay (Bio-Rad Laboratories, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 50-75 mg of total membrane protein.

Example 5.

Radioligand Binding Assays for Modulators of Chimeric Receptors

Purified membranes from HEK 293 cells expressing the monkey MCH receptor are prepared by the procedure given in Example 3. The membrane homogenate is centrifuged as before and resuspended to a protein concentration of 333ug/ml in binding buffer (Wash buffer + 0.1% BSA and 1.0uM final conc. phosphoramidon) for an assay volume of 50ug membrane protein/150ul binding buffer. Phosphoramidon is from SIGMA BIOCHEMICALS, St. Louis, MO (cat# R-7385).

Competition binding assays are performed at room temperature in Falcon 96 well round bottom polypropylene plates. To each assay well is added: 150 ul of MCH receptor containing membranes in binding buffer, prepared as described above, 50 ul ^{125}I -Tyr MCH in binding buffer, 50 ul binding buffer, and 2 ul test compound in DMSO. ^{125}I -Tyr MCH (specific activity = 2200 Ci/mMol) is purchased from NEN, Boston, MA (Cat # NEX 373) and is diluted in binding buffer to provide a final assay concentration of 30 pM.

Non-specific binding is defined as the binding measured in the presence of 1 uM unlabeled MCH. MCH is purchased from BACHEM U.S.A., King of Prussia, PA (cat # H-1482). To each assay well used to determine non-specific MCH binding is added: 150 ul of MCH receptor-containing membranes in binding buffer, 50 ul ^{125}I -Tyr MCH in binding buffer, unlabeled MCH in 25 ul binding buffer, and 25 ul binding buffer.

Assay plates are incubated for 1 hour at room temperature. Membranes are harvested onto WALLAC glass fiber filters (PERKIN-ELMER, Gaithersburg, MD) which are pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters are allowed to dry overnight then counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT scintillation fluid.

For saturation binding the concentration of ^{125}I -Tyr MCH is varied from 7 – 1,000 pM. Typically 11 concentration points are collected per saturation binding curve.

Equilibrium binding parameters are determined by fitting the allosteric Hill equation to the measured values with the aid of the computer program FitP™ (BIOSOFT, Ferguson, MO).

5 **Example 6.**

Functional Assay of Monkey MCH receptors

Calcium mobilization assay

The following assay can be used to monitor the response of cells expressing melanin concentrating hormone receptors to melanin concentrating hormone. The assay can also be
10 used to determine if test compounds act as agonists or antagonists of melanin concentrating hormone receptors.

Chinese Hamster Ovary (CHO) cells stably transfected with an MCH 1 receptor expression vector are grown to a density of 15,000 cells/well in FALCON black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ). Prior to
15 running the assay the culture medium is emptied from the 96 well plates. Fluo-3 calcium sensitive dye (Molecular Probes, Eugene, OR) is added to each well (dye solution: 1 mg FLUO-3 AM, 440 μ L DMSO and 440 μ L 20% pluronic acid in DMSO, diluted 1:4, 50 μ L diluted solution per well). Plates are covered with aluminum foil and incubated at 37°C for 1-2 hours. After the incubation the dye solution is emptied from the plates, cells are washed
20 once in 100 μ L KRH buffer (0.05 mM KCl, 0.115 M NaCl, 9.6 mM NaH_2PO_4 , 0.01 mM MgSO_4 , 25 mM HEPES, pH 7.4) to remove excess dye; after washing 80 μ L KRH buffer is added to each well.

Determination of Agonist Effects

Fluorescence response may monitored upon the addition of either human MCH or test
25 compound as described below by a FLIPR™ plate reader (Molecular Devices, Sunnyvale, CA) by excitation at 480 nM and emission at 530 nM.

Determination of Antagonist Effects

In order to measure the ability of a test compound to antagonize the response of cells expressing MCH receptors to MCH, the EC_{50} of MCH is first determined.

30 An additional 20 μ L of KRH buffer and 1 μ L DMSO is added to each well of cells, prepared as described immediately above. 100 μ L human MCH in KRH buffer is automatically transferred by the FLIPR instrument to each well. An 8-point concentration response curve, with final MCH concentrations of 1 nM to 3 μ M, is used to determine MCH EC_{50} .

Test compounds are dissolved in DMSO, diluted in 20 μ L KRH buffer, and added to

cells prepared as described above. The 96 well plates containing prepared cells and test compounds are incubated in the dark, at room temperature for 0.5 – 6 hours. It is important that the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response 100 ul human MCH diluted in KRH buffer to 2 x EC₅₀ is automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 ul and a final MCH concentration of EC₅₀. The final concentration of test compounds in the assay wells is between 1 uM and 5 uM. Typically cells exposed to one EC₅₀ of MCH exhibit a fluorescence response of about 10,000 Relative Fluorescence Units. Antagonists of the MCH receptor exhibit a response that is significantly less than that of the control cells to the p≤0.05 level, as measured using a parametric test of statistical significance. Typically antagonists of the MCH receptor decrease the fluorescence response relative to control cells by about 20%, preferably by about 50%, and most preferably by at least 80% as compared to matched controls.

Determination of Agonist Effects

The ability of a compound to act as an agonist of the MCH receptor may be determined by measuring the fluorescence response of cells expressing MCH receptors, using the methods described above, in the absence of MCH. Compounds that cause cells to exhibit fluorescence above background are MCH 1 receptor agonists.

Example 7

Preparation of radiolabeled probe compounds of the invention

The compounds of the invention are prepared as radiolabeled probes by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ¹⁴C), hydrogen (preferably ³H), sulfur (preferably ³⁵S), or iodine (preferably ¹²⁵I). Such radiolabeled probes are conveniently synthesized by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds. Such suppliers include Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravek Biochemicals Inc., Brea, CA.

Tritium labeled probe compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations

are also conveniently carried out as a custom radiolabeling by any of the suppliers listed in the preceding paragraph using the compound of the invention as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

5

Example 8

Use of compounds of the invention as probes for melanin receptors in cultured cells and tissue samples

Receptor autoradiography (receptor mapping) of melanin concentrating hormone
10 receptors in cultured cells or tissue samples is carried out in vitro as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York, using radiolabeled compounds of the invention prepared as described in the preceding Example.

15 Example 9

Determination of D₂ and D₄ receptor binding activity

The following assay is a standard assay for determining the binding affinity of compounds to dopamine D₄ and D₂ receptors.

Pellets of Chinese hamster ovary (CHO) cells containing recombinantly expressing
20 primate D₂, human D₄ dopamine receptors are used for the assays. The sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer containing 120 mM NaCl, 5 mM MgCl₂ and 1 mM EDTA at 4°C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described and the final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris
25 HCl buffer containing 120 mM NaCl.

Incubations for dopaminergic binding are carried out at 25°C and contain 0.4 ml of tissue sample, 0.1 nM ³H-YM 09151-2 (Nemonapride, cis-5-Chloro-2-methoxy-4-(methylamino)-N-(2-methyl-2-(phenylmethyl)-3-pyrrolidiny)benzamide) and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding is defined as that binding
30 found in the presence of 1 micromolar spiperone; without further additions, nonspecific binding is less than 20% of total binding.

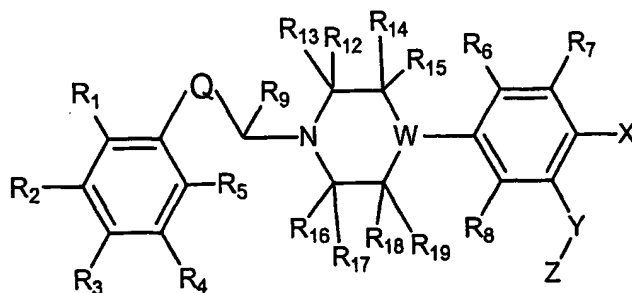
The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which

it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the invention and that modifications may be made therein without departing from the spirit or scope of the invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims

5 conclude this specification.

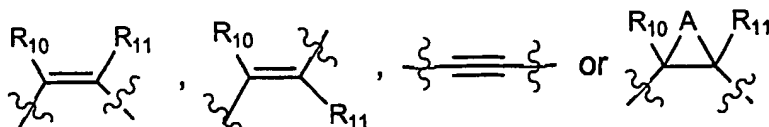
What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof wherein:

- 5 Q represents a group of the Formula:



wherein A is C₁-C₅ alkylene optionally mono-, di, or trisubstituted with substituents independently chosen from C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, halo(C₁-C₃)alkyl, halo(C₁-C₃)alkoxy, hydroxy, amino, and mono- or di(C₁-C₃)alkylamino;

- 10 R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ are the same or different and represent hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -SO₂NH₂, mono or dialkylsulfonamido, -C(O)NH₂, or mono or di(C₁-C₆)alkylcarboxamido;
- 15 R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ independently represent hydrogen or C₁-C₆ alkyl;

W is nitrogen or C-R_a where R_a represents hydrogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl or cyano;

X represents halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkylamino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -CONH₂, mono- or di(C₁-C₆)alkylcarboxamido, -SO₂NH₂, mono or di(C₁-C₆)alkylsulfonamido; or

X represents phenyl which may be optionally substituted with up to five substituents, which are the same or different and are selected from the group consisting of hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-

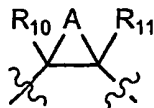
C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxy carbonyl, -COOH, -CONH₂, mono- or di-(C₁-C₆)alkylcarboxamido, -SO₂NH₂, and mono or di(C₁-C₆)alkylsulfonamido;

Y is oxygen, sulfur, -S(O)-, or -SO₂-; and

Z is C₁-C₆ alkyl or mono, di or trifluoromethyl.

5

2. A compound or salt according to claim 1, wherein Q is a group of the Formula:



and A is methylene optionally substituted with C₁-C₂ alkyl.

10

3. A compound or salt according to claim 2, wherein A is methylene and W is nitrogen.

4. A compound or salt according to claim 3, wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen.

15

5. A compound or salt according to claim 4, wherein:

wherein

X is halogen;

Y is oxygen; and

20 Z is C₁-C₆ alkyl.

6. A compound or salt according to claim 4, wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

25 X is hydrogen, halogen, or phenyl;

Y is oxygen; and

Z is C₁-C₆ alkyl.

7. A compound or salt according to claim 4, wherein:

30 R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

X is halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

8. A compound or salt according to claim 2, wherein A is methylene and W is
5 CH.

9. A compound or salt according to claim 8, wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅,
R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen.

- 10 10. A compound or salt according to claim 9, wherein:

X is halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

- 15 11. A compound or salt according to claim 9, wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen,
halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

X is hydrogen, halogen, or phenyl;

Y is oxygen; and

- 20 Z is C₁-C₆ alkyl.

12. A compound or salt according to claim 9, wherein:

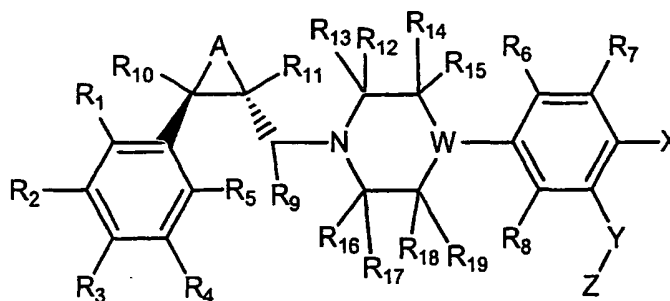
R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen,
halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

- 25 X is halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

13. A compound or salt according to Claim 2, of the formula



where A is methylene optionally substituted with C₁-C₂ alkyl.

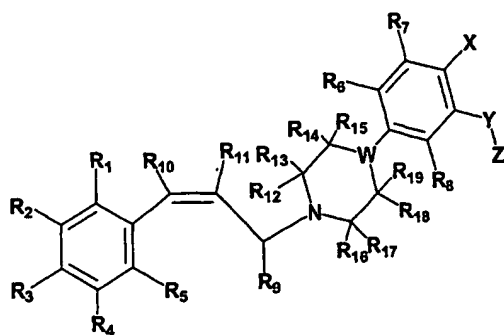
14. A compound or salt according to Claim 13, wherein A is methylene and W is
5 nitrogen or CH.

15. A compound or salt according to claim 14, wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₅, R₁₇,
R₁₈, and R₁₉ are hydrogen.

10 16. A compound or salt according to claim 15, wherein
R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ independently represent hydrogen, halogen, C₁-C₆ alkyl, C₁-
C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;
R₁₄ and R₁₆ are the same or different and are either hydrogen or methyl;
X is hydrogen, halogen, or phenyl;
15 Y is oxygen; and
Z is C₁-C₆ alkyl.

17. A compound or salt according to Claim 14, wherein
R₁, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ are hydrogen;
20 R₂, R₃, R₄, and R₅ are independently hydrogen, C₁-C₂ alkyl, C₁-C₂ alkoxy, or halogen;
X is halogen;
Y is oxygen; and
Z is C₁-C₆ alkyl.

25 18. A compound or salt according to claim 1 of the formula



19. A compound or salt according to claim 18, wherein:

5 R₁₃, R₁₅, R₁₇, R₁₉, are hydrogen; and

R₁₀, R₁₁, R₁₂, R₁₄, R₁₆, and R₁₈ independently represent hydrogen or methyl.

20. A compound or salt according to claim 19, wherein R₁₀, R₁₁, R₁₂, R₁₄, R₁₆, and R₁₈ are hydrogen.

10

21. A compound or salt according to claim 20, wherein W is N or CH.

22. A compound or salt according to claim 21, wherein:

R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ independently represent hydrogen, halogen, C₁-C₆ alkyl,

15 C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

X is hydrogen or halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

20 23. A compound or salt according to claim 21, wherein:

R₁, R₂, R₃, R₄ independently represent hydrogen, halogen, C₁-C₂alkyl, or C₁-C₂ alkoxy;

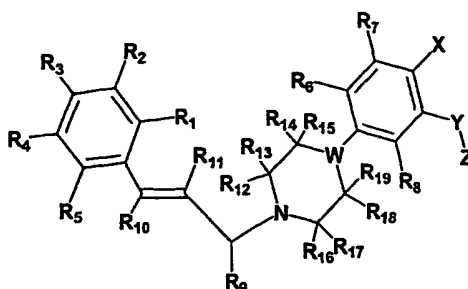
R₅, R₆, R₇, and R₈ are hydrogen;

X is halogen;

Y is oxygen; and

25 Z is C₁-C₆ alkyl.

24. A compound or salt according to claim 1, of the formula



25. A compound or salt according to claim 24, wherein:

R₁₃, R₁₅, R₁₇, R₁₉, are hydrogen; and

5 R₁₀, R₁₁, R₁₂, R₁₄, R₁₆, and R₁₈ independently represent hydrogen or methyl.

26. A compound or salt according to claim 25, wherein R₁₀, R₁₁, R₁₂, R₁₄, R₁₆, and

R₁₈ are hydrogen.

10 27. A compound or salt according to claim 26, wherein W is N or CH.

28. A compound or salt according to claim 27 wherein

R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ independently represent hydrogen, halogen, C₁-C₆ alkyl,

C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

15 X is hydrogen or halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

29. A compound or salt according to Claim 27 wherein

20 R₁, R₂, R₃, R₄ independently represent hydrogen, halogen, C₁-C₂alkyl, or C₁-C₂ alkoxy;

R₅, R₆, R₇, and R₈ are hydrogen;

X is halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

25 30. A compound or salt according to Claim 1, which is selected from:

1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine;

(1*S*, 2*S*)-1-(4-bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl)methylpiperazine;

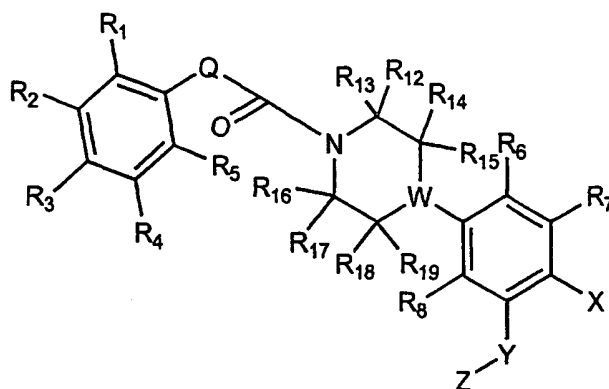
- 1R, 2R-1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine;
1-(4-Iodo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine;
1-(4-Chloro-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine;
1-(4-Phenyl-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperazine;
5 1-(4-Bromo-3-methoxyphenyl)-4-[*trans*-2-(3-methoxyphenyl)cyclopropyl] methylpiperazine;
1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-[4-chlorophenyl] cyclopropyl) methylpiperazine;
1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-[2-methylphenyl] cyclopropyl)methylpiperazine;
1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-[4-methoxyphenyl] cyclopropyl)methylpiperazine;
1-(4-Bromo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine;
10 1-(4-Iodo-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine;
1-(4-Chloro-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine;
1-(4-Methyl-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine;
1-(4-Trifluormethyl-3-methoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine; and
1-(4-Bromo-3-ethoxyphenyl)-4-(*trans*-2-phenylcyclopropyl) methylpiperidine; or a
15 pharmaceutically acceptable salt thereof.

31. A compound or salt according to Claim 1, which is selected from:

- 1-(4-Bromo-3-methoxyphenyl)-4-([3-phenyl]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{2-methylphenyl}]propen-2-yl)piperazine;
20 1-(3-Methoxyphenyl)-4-([3-phenyl]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{3-methylphenyl}]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{2-methoxyphenyl}]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{3-chlorophenyl}]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{3-ethoxyphenyl}]propen-2-yl)piperazine;
25 1-(4-Bromo-3-methoxyphenyl)-4-([3-{2,3-dimethoxyphenyl}]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{3,4-dimethoxyphenyl}]propen-2-yl)piperazine;
1-(4-Bromo-3-methoxyphenyl)-4-([3-{2,5-dimethoxyphenyl}]propen-2-yl)piperazine; and
1-(4-Bromo-3-methoxyphenyl)-4-([3-{2,4-dimethoxyphenyl}]propen-2-yl)piperazine, or a
pharmaceutically acceptable salt thereof.

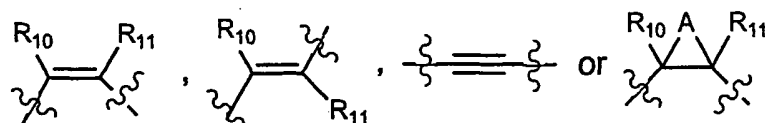
30

32. A compound of the formula:



wherein:

Q represents a group of the Formula:



- 5 wherein A is C₁-C₅ alkylene optionally mono-, di, or trisubstituted with substituents independently chosen from C₁-C₃ alkyl, C₁-C₃ alkoxy, halogen, halo(C₁-C₃)alkyl, halo(C₁-C₃)alkoxy, hydroxy, amino, and mono- or di(C₁-C₃)alkylamino;
- R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ are the same or different and represent hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -SO₂NH₂, mono or dialkylsulfonamido, -C(O)NH₂, or mono or di(C₁-C₆)alkylcarboxamido;
- 10 R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, and R₁₉ independently represent hydrogen or C₁-C₆ alkyl;
- 15 W is nitrogen or C-R_a where R_a represents hydrogen, hydroxy, C₁-C₆ alkoxy, C₁-C₆ alkyl or cyano;
- X represents halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkylamino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy, C₁-C₆ alkanoyl, C₁-C₆ alkoxycarbonyl, -COOH, -CONH₂, mono or di(C₁-C₆)alkylcarboxamido, -SO₂NH₂, mono or di(C₁-C₆)alkylsulfonamido; or
- 20 X represents phenyl which may be optionally substituted by up to five substituents, which may be the same or different and are selected from the group consisting of hydrogen, halogen, cyano, nitro, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ alkoxy, C₁-C₆

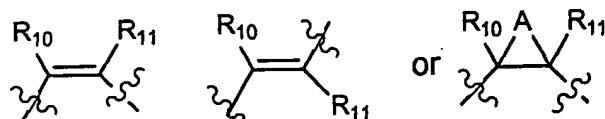
alkylthio, hydroxy, amino, mono or di(C₁-C₆)alkyl amino, halo(C₁-C₆)alkyl, halo(C₁-C₆)alkoxy,

C₁-C₆ alkanoyl, C₁-C₆ alkoxy, -COOH, -CONH₂, mono- or di-(C₁-C₆)alkylcarboxamido, -SO₂NH₂, and mono or di(C₁-C₆)alkylsulfonamido;

5 Y is oxygen, sulfur, -S(O)-, or -SO₂-; and

Z is C₁-C₆ alkyl or mono, di or trifluoromethyl.

33. A compound or salt according to claim 32, wherein Q is a group the formula



10 where A is methylene optionally substituted with C₁-C₂ alkyl or A is a single bond.

34. A compound according to claim 32, wherein W is nitrogen or CH.

35. A compound according to claim 34, wherein R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇,

15 R₁₈, and R₁₉ are hydrogen.

36. A compound according to claim 35 wherein:

X is halogen;

Y is oxygen; and

20 Z is C₁-C₆ alkyl.

37. A compound according to Claim 35 wherein

R₁, R₂, R₃, R₄, R₅, R₆, R₇, and R₈ may be the same or different and represent hydrogen, halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, trifluoromethyl, or trifluoromethoxy;

25 X is halogen;

Y is oxygen; and

Z is C₁-C₆ alkyl.

38. A pharmaceutical composition comprising a compound or salt according Claim 1

30 combined with at least one pharmaceutically acceptable carrier or excipient.

39. The pharmaceutical composition of Claim 38 wherein the pharmaceutical composition is formulated as an injectable fluid, a pill, a capsule, a syrup, or a transdermal patch.

5 40. A method for the treatment of obesity, said method comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of Claim 1.

41. A method for demonstrating the presence of MCH 1 receptors in cell or tissue
10 samples, said method comprising:

preparing a plurality of matched cell or tissue samples,

preparing at least one control sample by contacting under conditions that permit binding of MCH to MCH 1 receptors within cell and tissue samples at least one of the matched cell or tissue samples with a control solution comprising a detectably-labeled
15 preparation of a selected compound or salt of Claims 1 at a first measured molar concentration, said control solution further comprising an unlabelled preparation of the selected compound or salt at a second measured molar concentration, which second measured concentration is greater than said first measured concentration,

preparing at least one experimental sample by contacting under conditions that permit
20 binding of MCH to MCH 1 receptors within cell and tissue samples at least one of the matched cell or tissue samples with an experimental solution comprising the detectably-labeled preparation of the selected compound or salt at the first measured molar concentration, said experimental solution not further comprising an unlabelled preparation of any compound or salt of any of Claim 1 at a concentration greater than or equal to said first
25 measured concentration;

washing the at least one control sample to remove unbound selected compound or salt to produce at least one washed control sample;

washing the at least one experimental sample to remove unbound selected compound or salt to produce at least one washed experimental sample;

30 measuring the amount of detectable label of any remaining bound detectably-labeled selected compound or salt in the at least one washed control sample;

measuring the amount detectable label of any remaining bound detectably-labeled selected compound or salt in the at least one washed experimental sample;

comparing the amount of detectable label measured in each of the at least one washed experimental sample to the amount of detectable label measured in each of the at least one washed control sample

wherein, a comparison that indicates the detection of a greater amount of detectable label in the at least one washed experimental sample than is detected in any of the at least one washed control samples demonstrates the presence of MCH 1 receptors in that experimental sample.

42. The method of Claim 41 wherein the compound is radiolabeled.

43. The method of Claim 42 wherein the detection is accomplished using autoradiography.

44. A method for altering the signal-transducing activity of MCH 1 receptors, said method comprising contacting cells expressing such receptors with a solution comprising a compound according to Claim 1 at a concentration sufficient to detectably alter the electrophysiology of the cell, wherein a detectable alteration of the electrophysiology of the cell indicates an alteration of the signal-transducing activity of MCH 1 receptors.

45. The method of Claim 44 wherein the cell is a neuronal cell that is contacted in vivo in an animal, the solution is a body fluid, and the alteration in the electrophysiology of the cell is detected as a reproducible change in the animal's feeding behavior.

46. The method of Claim 45 wherein the animal is a human, the cell is a brain cell, and the fluid is cerebrospinal fluid.

47. A packaged pharmaceutical composition comprising the pharmaceutical composition of Claim 38 in a container and instructions for using the composition to treat a patient suffering from obesity.

48. The use of a compound according to any one of claims 1-37 in the preparation of a medicament for use in the treatment of obesity.

-2-

that fasting further increased MCH mRNA in both obese and normal mice during fasting. MCH also stimulated feeding in normal rats when injected into the lateral ventricles (Rossi et al., 1997). MCH also has been reported to functionally antagonize the behavioral effects of α -MSH (Miller et al., 1993; Gonzalez et al., 1996; Sanchez et al., 1997); in addition, stress has been shown to increase POMC mRNA levels while decreasing the MCH precursor preproMCH (ppMCH) mRNA levels (Presse et al., 1992). Thus MCH may serve as an integrative neuropeptide involved in the reaction to stress, as well as in the regulation of feeding and sexual activity (Baker, 1991; Knigge et al., 1996).

Although the biological effects of MCH are believed to be mediated by specific receptors, binding sites for MCH have not been well described. A tritiated ligand ($[^3\text{H}]\text{-MCH}$) was reported to exhibit specific binding to brain membranes but was unusable for saturation analyses, so neither affinity nor B_{max} were determined (Drozd and Eberle, 1995). Radioiodination of the tyrosine at position thirteen resulted in a ligand with dramatically reduced biological activity (see Drozd and Eberle, 1995). In contrast, the radioiodination of the MCH analogue $[\text{Phe}^{13}, \text{Tyr}^{19}]\text{-MCH}$ was successful (Drozd et al., 1995); the ligand retained biological activity and exhibited specific binding to a variety of cell lines including mouse melanoma (B16-F1, G4F, and G4F-7), PC12, and COS cells. In G4F-7 cells, the $K_D = 0.118\text{nM}$ and the $B_{\text{max}} \sim 1100$ sites/cell. Importantly, the binding was not inhibited by α -MSH but was weakly inhibited by rat ANF ($K_i = 116\text{ nM}$ vs. 12 nM for native MCH) (Drozd et al., 1995). More recently specific MCH binding was reported in transformed keratinocytes (Burgaud et al., 1997) and melanoma cells (Drozd et al., 1998), where photo-crosslinking studies suggest that the receptor is a membrane protein with an apparent molecular weight of 45-50

-3-

kDaltons, compatible with the molecular weight range of the GPCR superfamily of receptors. No radioautoradiographic studies of MCH receptor localization using this ligand have been reported as yet.

5

The localization and biological activities of MCH peptide suggest that the modulation of MCH receptor activity may be useful in a number of therapeutic applications. The role of MCH in feeding is the best characterized of its potential clinical uses. MCH is expressed in the lateral hypothalamus, a brain area implicated in the regulation of thirst and hunger (Grillon et al., 1997); recently orexins A and B, which are potent orexigenic agents, have been shown to have very similar localization to MCH in the lateral hypothalamus (Sakurai et al., 1998). MCH mRNA levels in this brain region are increased in rats after 24 hours of food-deprivation (Hervé and Fellman, 1997); after insulin injection, a significant increase in the abundance and staining intensity of MCH immunoreactive perikarya and fibres was observed concurrent with a significant increase in the level of MCH mRNA (Bahjaoui-Bouhaddi et al., 1994). Consistent with the ability of MCH to stimulate feeding in rats (Rossi et al., 1997) is the observation that MCH mRNA levels are upregulated in the hypothalami of obese *ob/ob* mice (Qu et al., 1996), and decreased in the hypothalami of rats treated with leptin, whose food intake and body weight gains are also decreased (Sahu, 1998). MCH appears to act as a functional antagonist of the melanocortin system in its effects on food intake and on hormone secretion within the HPA (hypothalamopituitary/adrenal axis) (Ludwig et al., 1998). Together these data suggest a role for endogenous MCH in the regulation of energy balance and response to stress, and provide a rationale for the development of specific compounds acting at MCH receptors for use in the treatment of obesity and stress-related disorders.

35

In all species studied to date, a major portion of the neurons of the MCH cell group occupies a rather constant location in those areas of the lateral hypothalamus and subthalamus where they lie and may be a part of some of the so-called "extrapyramidal" motor circuits. These involve substantial striato- and pallidofugal pathways involving the thalamus and cerebral cortex, hypothalamic areas, and reciprocal connections to subthalamic nucleus, substantia nigra, and mid-brain centers (Bittencourt et al., 1992). In their location, the MCH cell group may offer a bridge or mechanism for expressing hypothalamic visceral activity with appropriate and coordinated motor activity. Clinically it may be of some value to consider the involvement of this MCH system in movement disorders, such as Parkinson's disease and Huntingdon's Chorea in which extrapyramidal circuits are known to be involved.

Human genetic linkage studies have located authentic hMCH loci on chromosome 12 (12q23-24) and the variant hMCH loci on chromosome 5 (5q12-13) (Pedeutour et al., 1994). Locus 12q23-24 coincides with a locus to which autosomal dominant cerebellar ataxia type II (SCA2) has been mapped (Auburger et al., 1992; Twells et al., 1992). This disease comprises neurodegenerative disorders, including an olivopontocerebellar atrophy. Furthermore, the gene for Darier's disease, has been mapped to locus 12q23-24 (Craddock et al., 1993). Darier's disease is characterized by abnormalities in keratinocyte adhesion and mental illnesses in some families. In view of the functional and neuroanatomical patterns of the MCH neural system in the rat and human brains, the MCH gene may represent a good candidate for SCA2 or Darier's disease. Interestingly, diseases with high social impact have been mapped to this locus. Indeed, the gene responsible for chronic or acute

-5-

forms of spinal muscular atrophies has been assigned to chromosome 5q12-13 using genetic linkage analysis (Melki et al., 1990; Westbrook et al., 1992). Furthermore, independent lines of evidence support the assignment of a major schizophrenia locus to chromosome 5q11.2-13.3 (Sherrington et al., 1988; Bassett et al., 1988; Gilliam et al., 1989). The above studies suggest that MCH may play a role in neurodegenerative diseases and disorders of emotion.

Additional therapeutic applications for MCH-related compounds are suggested by the observed effects of MCH in other biological systems. For example, MCH may regulate reproductive functions in male and female rats. MCH transcripts and MCH peptide were found within germ cells in testes of adult rats, suggesting that MCH may participate in stem cell renewal and/or differentiation of early spermatocytes (Hervieu et al., 1996). MCH injected directly into the medial preoptic area (MPOA) or ventromedial nucleus (VMN) stimulated sexual activity in female rats (Gonzalez et al., 1996). In ovariectomized rats primed with estradiol, MCH stimulated luteinizing hormone (LH) release while anti-MCH antiserum inhibited LH release (Gonzalez et al., 1997). The zona incerta, which contains a large population of MCH cell bodies, has previously been identified as a regulatory site for the pre-ovulatory LH surge (MacKenzie et al., 1984). MCH has been reported to influence release of pituitary hormones including ACTH and oxytocin. MCH analogues may also be useful in treating epilepsy. In the PTZ seizure model, injection of MCH prior to seizure induction prevented seizure activity in both rats and guinea pigs, suggesting that MCH-containing neurons may participate in the neural circuitry underlying PTZ-induced seizure (Knigge and Wagner, 1997). MCH has also been observed to affect

-6-

behavioral correlates of cognitive functions. MCH treatment hastened extinction of the passive avoidance response in rats (McBride et al., 1994), raising the possibility that MCH receptor antagonists may be beneficial for memory storage and/or retention. A possible role for MCH in the modulation or perception of pain is supported by the dense innervation of the periaqueductal grey (PAG) by MCH-positive fibers. Finally, MCH may participate in the regulation of fluid intake. ICV infusion of MCH in conscious sheep produced diuretic, natriuretic, and kaliuretic changes in response to increased plasma volume (Parkes, 1996). Together with anatomical data reporting the presence of MCH in fluid regulatory areas of the brain, the results indicate that MCH may be an important peptide involved in the central control of fluid homeostasis in mammals.

As used in this invention, the term "antagonist" refers to a compound which binds to, and decreases the activity of, a receptor in the presence of an agonist. In the case of a G-protein coupled receptor, activation may be measured using any appropriate second messenger system which is coupled to the receptor in a cell or tissue in which the receptor is expressed. Some specific, but by no means limiting, examples of well-known second messenger systems are adenylate cyclase, intracellular calcium mobilization, ion channel activation, guanylate cyclase and inositol phospholipid hydrolysis. Conversely, the term "agonist" refers to a compound which binds to, and increases activity of, a receptor as compared with the activity of the receptor in the absence of any agonist.

In one embodiment of this invention, the synthesis of novel compounds which bind selectively to the cloned human melanin-concentrating hormone-1 (MCH1) receptor, compared

-7-

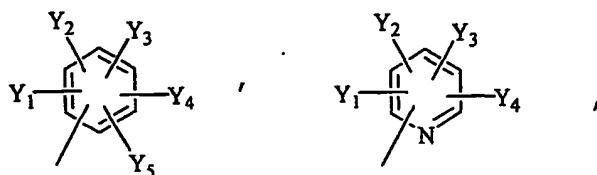
to other cloned G-protein coupled receptors, and inhibit the activation of the cloned receptors as measured in in vitro assays is disclosed. The in vitro receptor binding and activation assays described hereinafter were performed using various cultured cell lines, each transfected with and expressing only a single cloned receptor.

Furthermore, the compounds of the present invention may also be used to treat abnormal conditions such as feeding disorders (obesity, bulimia and bulimia nervosa), sexual/reproductive disorders, depression, anxiety, depression and anxiety, epileptic seizure, hypertension, cerebral hemorrhage, congestive heart failure, sleep disturbances, or any condition in which antagonism of an MCH1 receptor may be beneficial. In addition, the compounds of the present invention may be used to reduce the body mass of a subject.

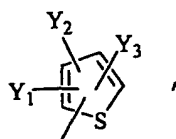
-9-

wherein A is

5

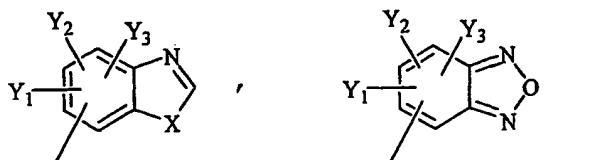


10



15

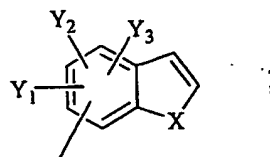
20



25

30

or



35

wherein each of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is independently -H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - NO_2 ; - N_3 ; -CN; - OR_3 , - $OCOR_3$, - COR_3 , - $CON(R_3)_2$, or - $COOR_3$; or any two of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 present on adjacent carbon atoms can constitute a methylenedioxy group;

45

wherein each X is independently S; O; or NR_3 ;

-10-

wherein R_1 is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; or -CO₂(CH₂)_nV;

wherein R_2 is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, -CH₂X(CH₂)_pNHCXR₇; or -OR₃; or wherein R_1 and R_2 together may form a lactone ring;

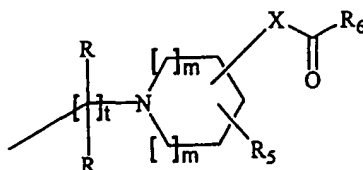
wherein each R_3 is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

25

wherein R_4 is

(i)

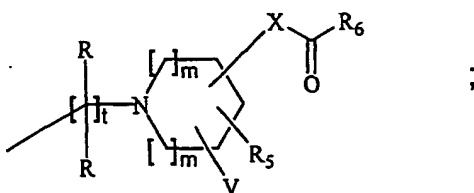
30



-11-

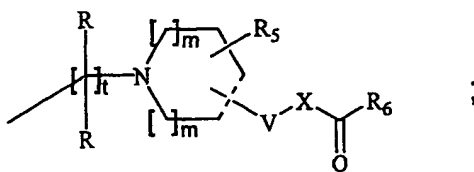
(ii)

5



(iii)

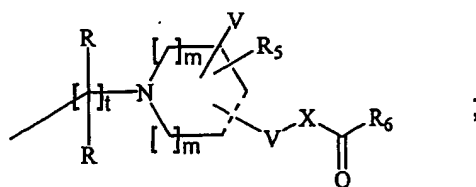
10



15

(iv)

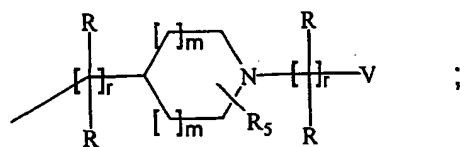
20



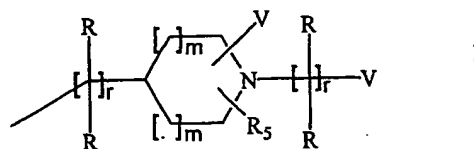
25

(v)

30



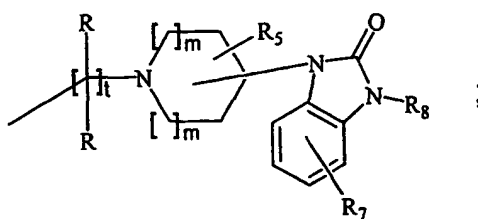
35 (vi)



40

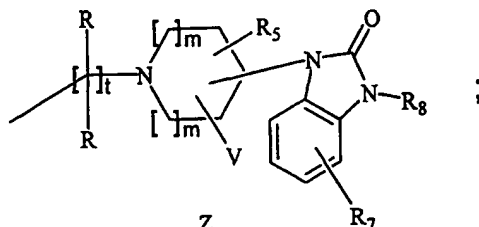
(vii)

45



(viii)

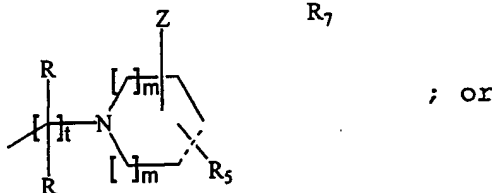
5



10

(ix)

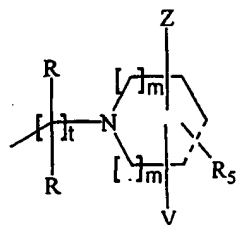
15



; or

(x)

20



;

25

wherein the dashed line represents a single bond or a double bond;

30

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or -CON(R₃)₂;

35

wherein each V is independently aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

40

-13-

wherein each R_5 is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_6 is -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_7 is H; F; Cl; Br; I; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or

-14-

-CON(R₃)₂;

wherein R₈ is independently straight chained or branched
C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight
5 chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein Z is naphthyl, quinolinyl, isoquinolinyl,
10 quinazolinyl, phthalazinyl, quinoxalinyl, indolyl,
benzo[b]furanyl, or benzo[b]thiophenyl; wherein the
naphthyl, quinolinyl, isoquinolinyl, quinazolinyl,
phthalazinyl, quinoxalinyl, indolyl, benzo[b]furanyl, or
benzo[b]thiophenyl may be substituted with one or more F;
15 Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
-SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched
C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,
or carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
20 monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein each m is independently an integer from 0 to 3
inclusive;

25 wherein each n is independently an integer from 0 to 5
inclusive;

wherein each p is independently an integer from 1 to 7
30 inclusive;

wherein q is an integer from 1 to 3 inclusive;

wherein r is an integer from 0 to 3 inclusive;
35

-15-

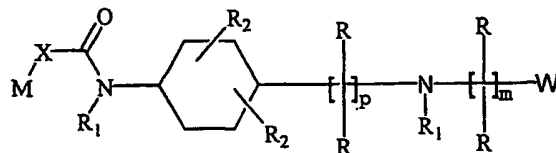
wherein t is an integer from 2 to 6 inclusive;

or a pharmaceutically acceptable salt thereof.

5

This invention further provides a compound having the structure:

10



15

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -SR₃; -CO₂R₃; or -OR₃;

20

wherein each R₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

25

wherein each R₂ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; or aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl,

35

-16-

monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
5 cycloalkenyl;

wherein each R₃ is independently -H; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
10 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl;

wherein M is aryl or heteroaryl, optionally substituted
with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN;
15 -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl;
C₃-C₇ cycloalkyl, monofluorocycloalkyl,
20 polyfluorocycloalkyl or cycloalkenyl;

wherein X is (CH₂)_n, O, S or NR₃;

wherein W is
25

(a) C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl optionally
substituted with one or more COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃;
30 straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl; or

35 (b) aryl or heteroaryl optionally substituted with one

-17-

or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN;
 -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃;
 straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
 5 carboxamidoalkyl; straight chained or branched C₂-C₇
 alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl;

wherein m is an integer from 0 to 4 inclusive;

10 wherein n is an integer from 0 to 6 inclusive;

wherein p is an integer from 1 to 4 inclusive;

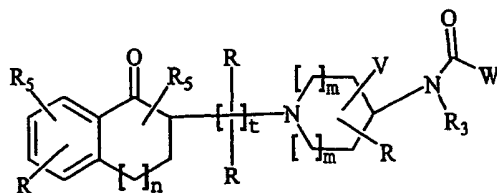
wherein q is an integer from 1 to 3 inclusive;

15

or a pharmaceutically acceptable salt thereof.

This invention also provides a compound having the
 structure:

20



25

wherein each R is independently -H; -F; straight chained
 or branched C₁-C₇ alkyl, monofluoroalkyl or
 polyfluoroalkyl; straight chained or branched C₂-C₇
 30 alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or
 -CON(R₃)₂;

wherein each R₁ is independently -H; F; Cl; Br; I; -NO₂;
 -N₃; -CN; straight chained or branched C₁-C₇ alkyl,
 35 monofluoroalkyl or polyfluoroalkyl; straight chained or
 branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or

-18-

cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$;
 $-CON(R_3)_2$; aryl or heteroaryl, wherein the aryl or
heteroaryl is optionally substituted with one or more F;
Cl; Br; I; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN; $-NO_2$; $-N(R_3)_2$; $-OR_3$;
5 $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained or branched
 C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,
or carboxamidoalkyl; straight chained or branched C_2-C_7
alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
10 cycloalkenyl;

wherein each R_3 is independently -H; straight chained or
branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-
15 C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl;

wherein R_5 is -H; $-NO_2$; $-N_3$; $-CN$; straight chained or
branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl;
20 straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-
 C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$;
 $-CON(R_3)_2$; aryl or heteroaryl, wherein the aryl or
heteroaryl is optionally substituted with one or more F;
25 Cl; Br; I; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN; $-NO_2$; $-N(R_3)_2$; $-OR_3$;
 $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained or branched
 C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,
or carboxamidoalkyl; straight chained or branched C_2-C_7
alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl,
30 monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein V is H; aryl or heteroaryl, optionally
substituted with one or more F; Cl; Br; I; COR_3 ; CO_2R_3 ;
35 $-CON(R_3)_2$; CN; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$;

-19-

(CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein W is

- 10 (a) C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl optionally substituted with one or more COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
15 branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl; or
20 (b) aryl or heteroaryl optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇
25 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl;

30 wherein each m is independently an integer from 0 to 3 inclusive;

wherein n is an integer from 0 to 2 inclusive;

35 wherein p is an integer from 1 to 7 inclusive;

-20-

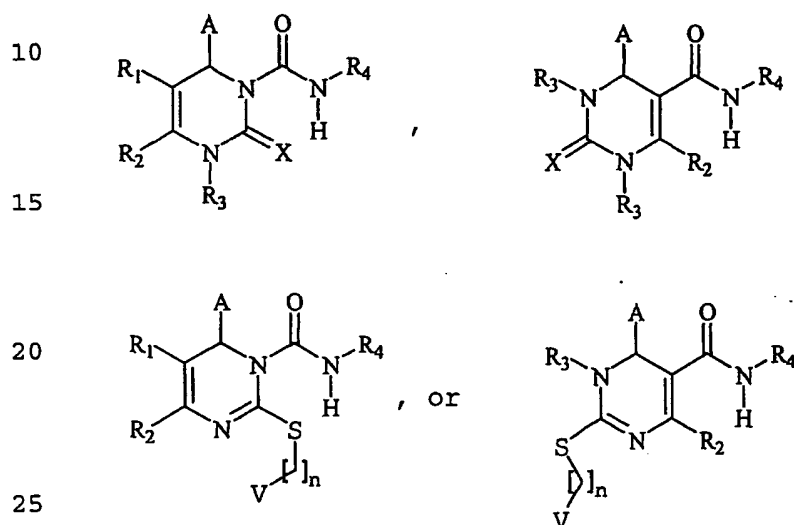
wherein q is an integer from 1 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

5 or a pharmaceutically acceptable salt thereof.

-21-

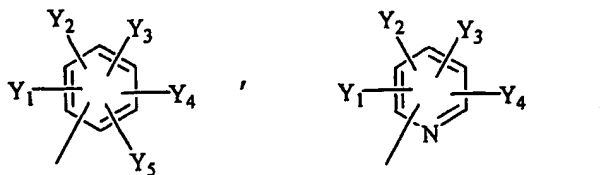
This invention further provides a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject wherein the compound has the structure:



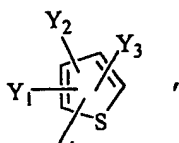
-22-

wherein A is

5

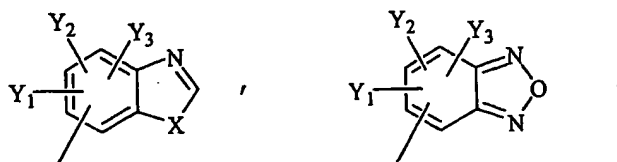


10



15

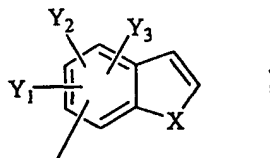
20



25

or

30



wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CON(R₃)₂, or -COOR₃; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each X is independently S; O; or NR₃;

45

wherein R₁ is -H; -NO₂; -CN; straight chained or branched

-23-

C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
5 -CON(R₃)₂; or CO₂(CH₂)_nV;

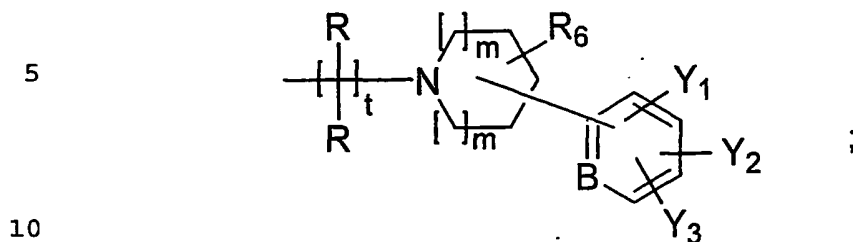
wherein R₂ is -H; straight chained or branched C₁-C₇
alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,
monofluoroalkyl or polyfluoroalkyl; straight chained or
10 branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀
cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-
C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃,
15 -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃,
-CH₂X(CH₂)_pNHCXR₅; -OR₃; or wherein R₁ and R₂ together form
a lactone ring;

wherein each R₃ is independently -H; straight chained or
20 branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl;

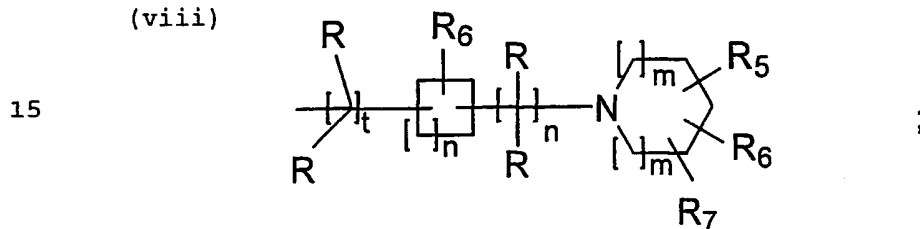
25

-25-

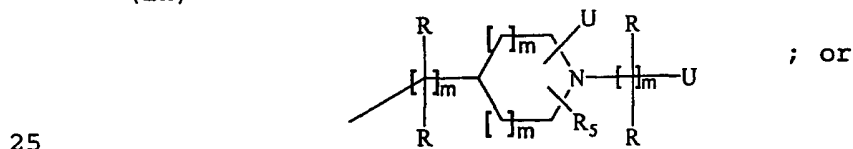
(vii)



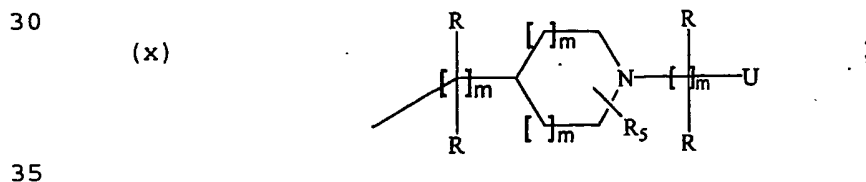
(viii)



(ix)



(x)



wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or -CN(R₃)₂;

wherein B is N or CY₄;

wherein each D is independently C(R₃)₂; O; S; NR₃; CO; or CS;

-26-

wherein each U is independently aryl or heteroaryl,
optionally substituted with one or more F; Cl; Br; I;
COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
(CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇
5 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

10

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

wherein W is CR₅; CR₆ or N;

15

wherein Z is S; O; C(R₃)₂; or NR₃;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
20 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein the
aryl or heteroaryl is optionally substituted with one or
more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
25 -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, or aminoalkyl; straight chained or
branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
30 cycloalkenyl;

35

wherein each R₆ is independently -H; straight chained or
branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl,
alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇

-27-

cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; or $-CON(R_3)_2$;

- 5 wherein R_7 is $-H$; aryl or heteroaryl, optionally substituted with one or more F ; Cl ; Br ; I ; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN ; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; $-XCOR_8$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
10 straight chained or branched C_2-C_7 alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

- wherein R_8 is $-H$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight
15 chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; or $-CON(R_3)_2$; aryl or heteroaryl, optionally substituted with
20 one or more F ; Cl ; Br ; I ; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN ; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or
25 branched C_2-C_7 alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein b is 1 or 2;

- 30 wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to 3 inclusive;

- 35 wherein each n is independently an integer from 0 to 5

-28-

inclusive;

wherein each p is independently an integer from 1 to 7
inclusive;

5

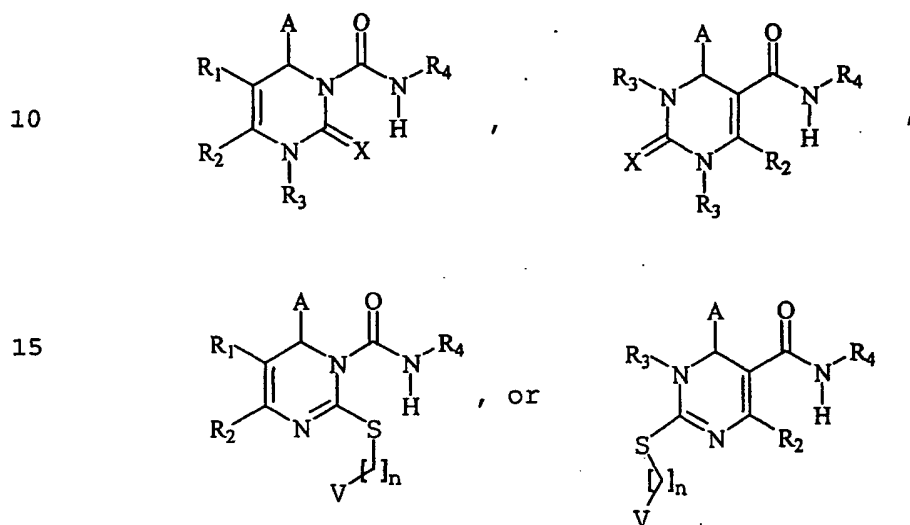
wherein q is an integer from 1 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

10 or a pharmaceutically acceptable salt thereof.

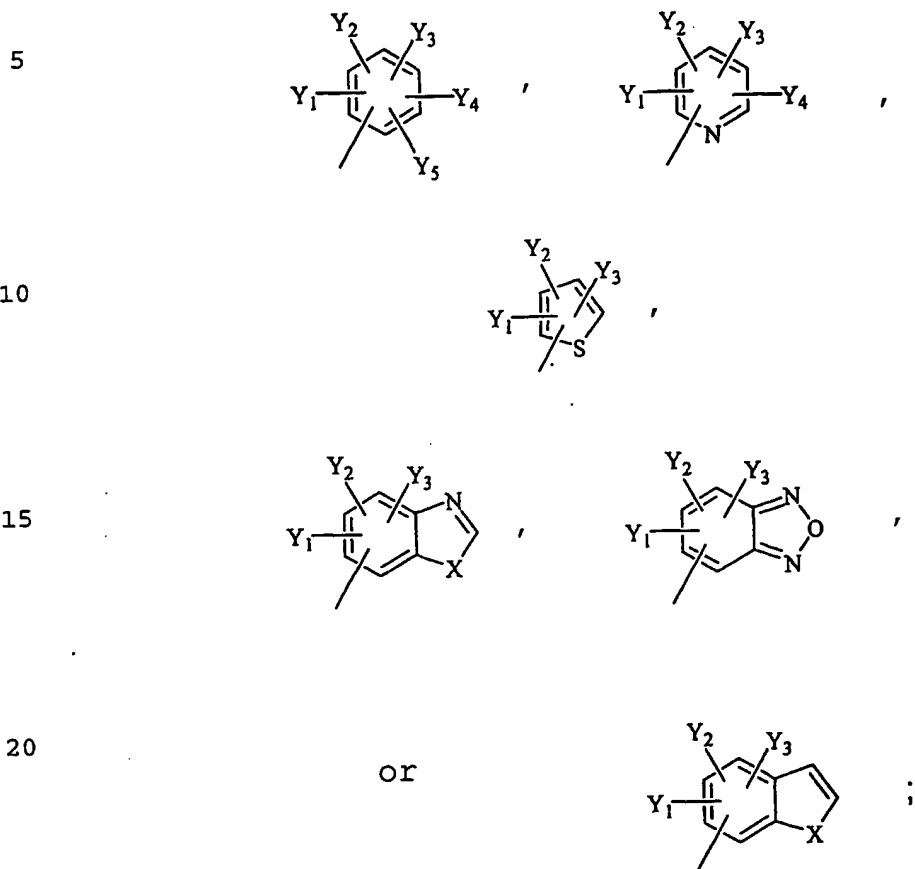
-29-

This invention further provides a method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound effective to reduce the body mass of the subject wherein the compound has the structure:



-30-

wherein A is



wherein each of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is independently -H;
 straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl
 or polyfluoroalkyl; straight chained or branched C_2 - C_7
 alkenyl or alkynyl; C_3 - C_7 cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl; -F, -Cl, -Br, or -I;
 - NO_2 ; - N_3 ; -CN; - OR_3 , - $OCOR_3$, - COR_3 , - $CON(R_3)_2$, or - $COOR_3$;
 or any two of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 present on adjacent
 carbon atoms can constitute a methylenedioxy group;

wherein each X is independently S; O; or NR_3 ;

-31-

wherein R_1 is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; or CO₂(CH₂)_nV;

wherein R_2 is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, -CH₂X(CH₂)_pNHCXR₅; -OR₃; or wherein R_1 and R_2 together form a lactone ring;

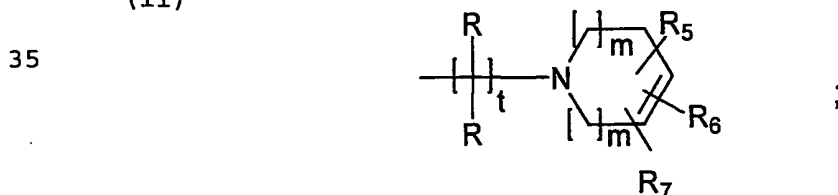
wherein each R_3 is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_4 is

(i)

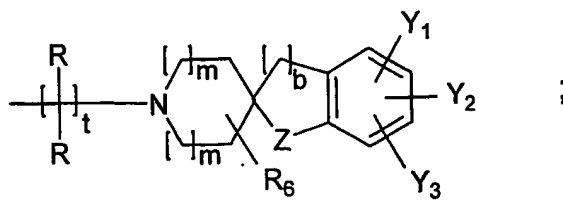


(ii)



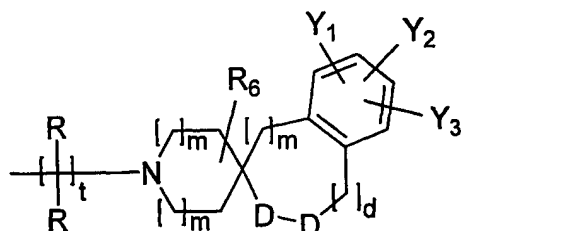
(iii)

5



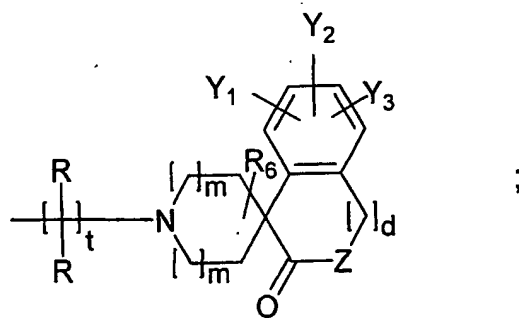
(iv)

10



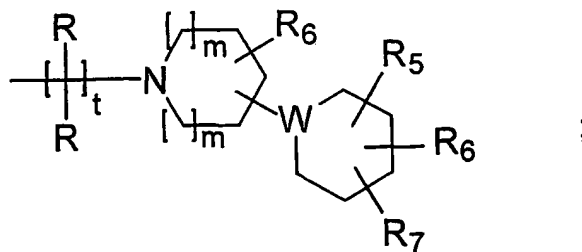
(v)

20

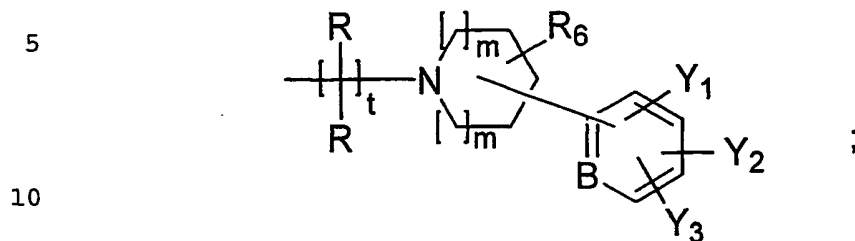


(vi)

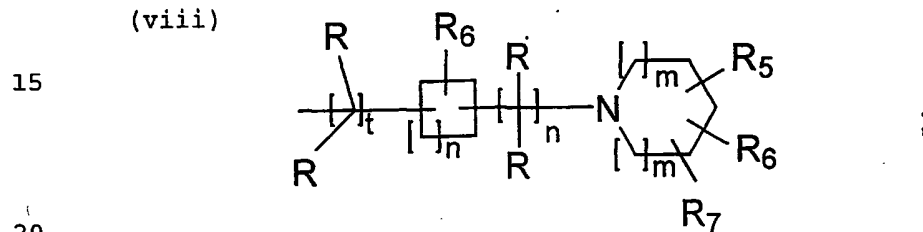
35



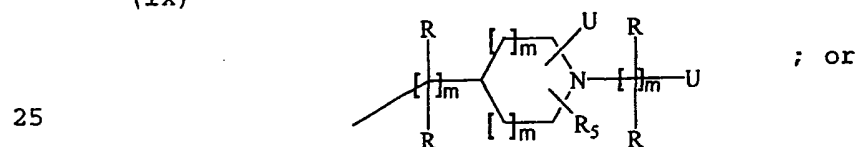
(vii)



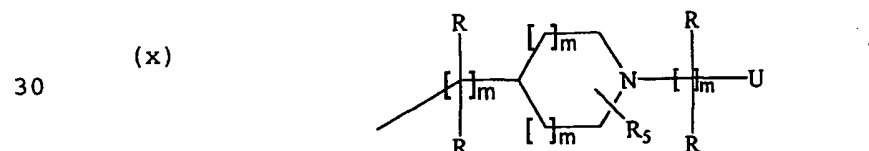
(viii)



(ix)



(x)



wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or -CN(R₃)₂;

wherein B is N or CY₄;

wherein each D is independently C(R₃)₂; O; S; NR₃; CO; or CS;

-34-

wherein each U is independently aryl or heteroaryl,
optionally substituted with one or more F; Cl; Br; I;
COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
(CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇
5 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

10

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

wherein W is CR₅; CR₆ or N;

15

wherein Z is S; O; C(R₃)₂; or NR₃;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
20 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein the
aryl or heteroaryl is optionally substituted with one or
more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
25 -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, or aminoalkyl; straight chained or
branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
30 cycloalkenyl;

wherein each R₆ is independently -H; straight chained or
branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl,
alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight
35 chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇

-35-

cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; or $-CON(R_3)_2$;

- 5 wherein R_7 is $-H$; aryl or heteroaryl, optionally substituted with one or more F ; Cl ; Br ; I ; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN ; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; $-XCOR_8$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
- 10 straight chained or branched C_2-C_7 alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

- 15 wherein R_8 is $-H$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; or $-CON(R_3)_2$; aryl or heteroaryl, optionally substituted with
- 20 one or more F ; Cl ; Br ; I ; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN ; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C_2-C_7 alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl,
- 25 monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein b is 1 or 2;

- 30 wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to 3 inclusive;

- 35 wherein each n is independently an integer from 0 to 5

-36-

inclusive;

wherein each p is independently an integer from 1 to 7
inclusive;

5

wherein q is an integer from 1 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

10

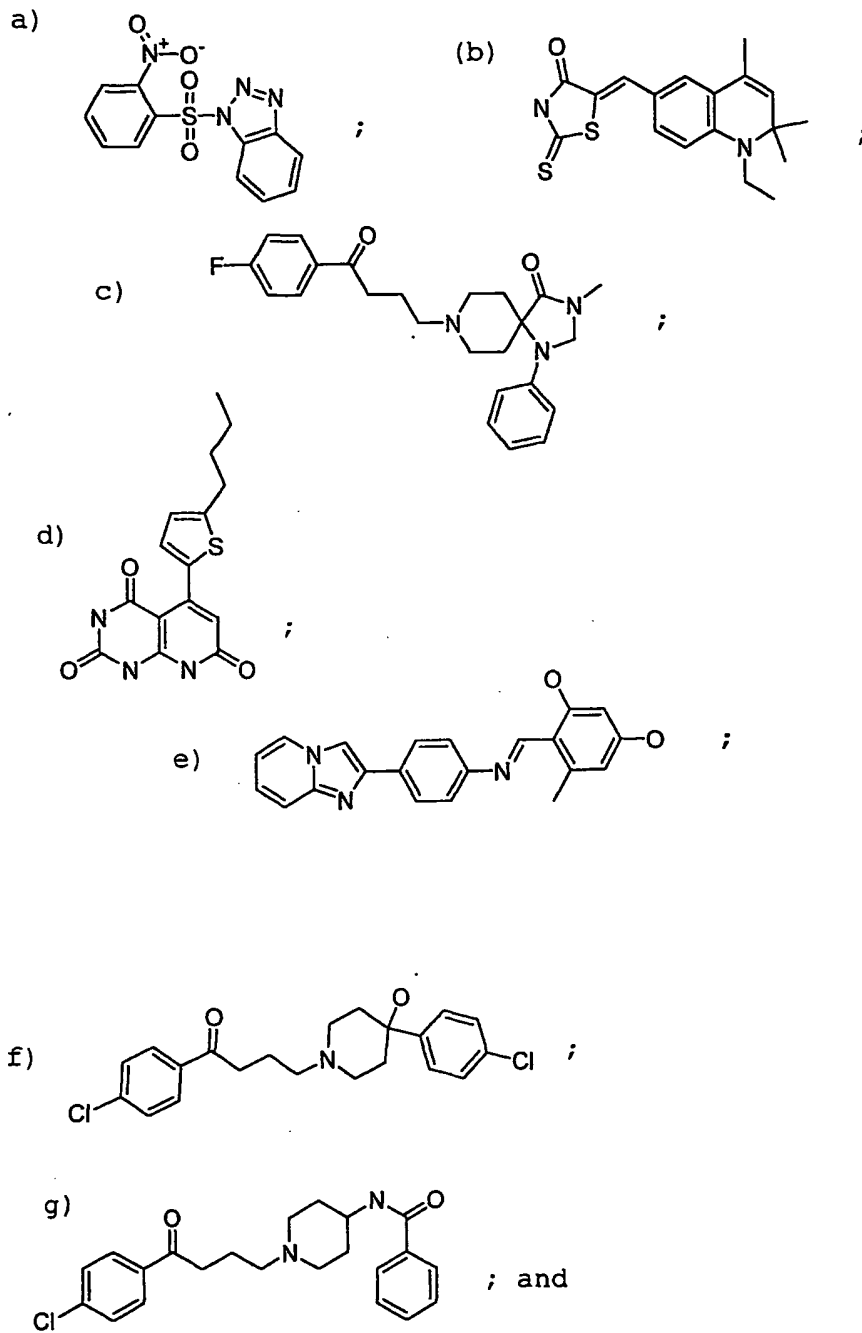
or a pharmaceutically acceptable salt thereof.

15

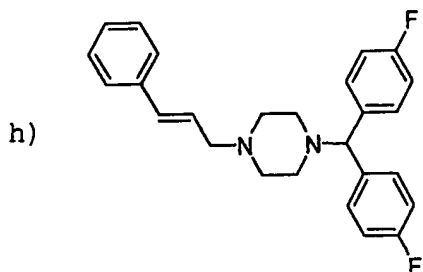
In addition, the present invention provides a method of
treating a subject suffering from depression and/or
anxiety which comprises administering to the subject a
compound of the aforementioned formula in an amount
effective to treat the subject's depression and/or
anxiety.

20

This invention also provides a method of modifying
feeding behavior of a subject which comprises
administering to the subject an amount of a compound
effective to decrease the consumption of food by the
subject wherein the compound is selected from the group
consisting of:



-38-



This invention further provides a method of treating a feeding disorder in a subject which comprises administering to the subject an amount of a compound of the invention effective to decrease the consumption of food by the subject.

This invention also provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier.

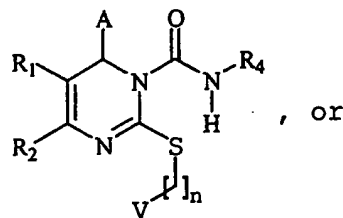
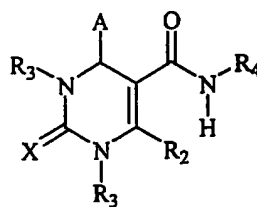
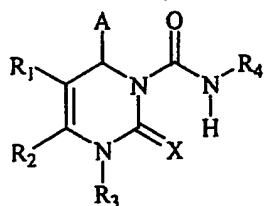
This invention further provides a pharmaceutical composition made by combining a therapeutically effective amount of the compound of this invention and a pharmaceutically acceptable carrier. This invention further provides a process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier.

Detailed Description Of The Invention

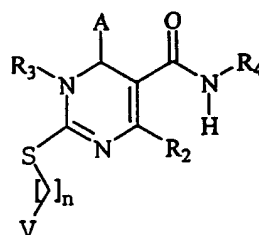
This invention provides a compound having the structure:

5

10

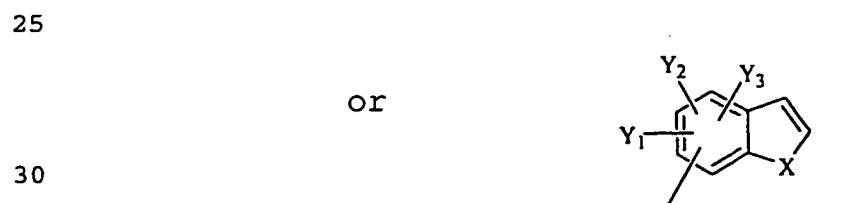
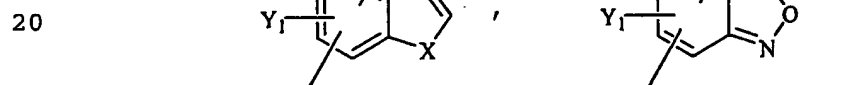
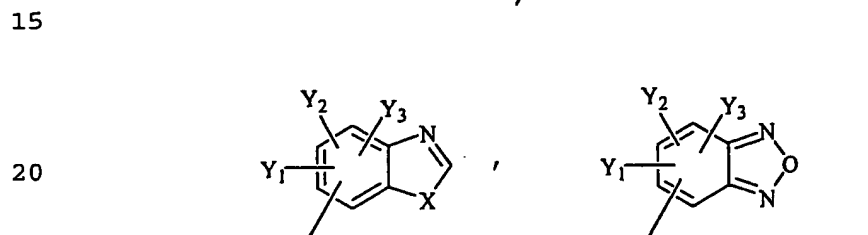
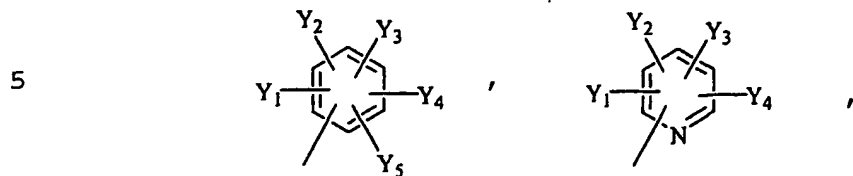


, or



-40-

wherein A is



wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H;
 35 straight chained or branched C₁-C₇ alkyl, monofluoroalkyl
 or polyfluoroalkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₃,
 40 -OCOR₃, -COR₃, -CON(R₃)₂, or -COOR₃; or any two of Y₁, Y₂,
 Y₃, Y₄ and Y₅ present on adjacent carbon atoms can
 constitute a methylenedioxy group;

wherein each X is independently S; O; or NR₃;
 45

wherein R₁ is -H; -NO₂; -CN; straight chained or branched

-41-

C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
5 -CON(R₃)₂; or -CO₂(CH₂)_nV;

wherein R₂ is -H; straight chained or branched C₁-C₇
alkyl, hydroxyalkyl, alkoxyalkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
10 alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀
cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-
C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃,
15 -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃,
-CH₂X(CH₂)_pNHCXR₇; -OR₃; or wherein R₁ and R₂ together form
a lactone ring;

wherein each R₃ is independently -H; straight chained or
20 branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl;

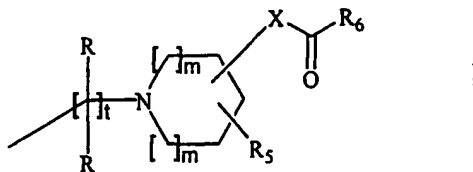
25

-42-

wherein R_4 is

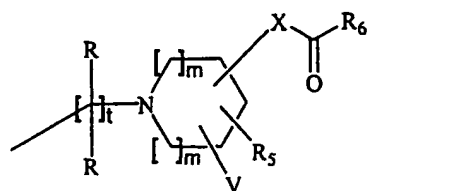
(i)

5



(ii)

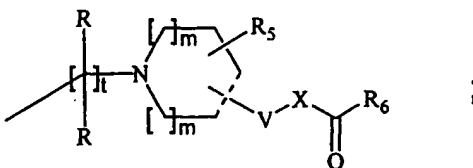
10



15

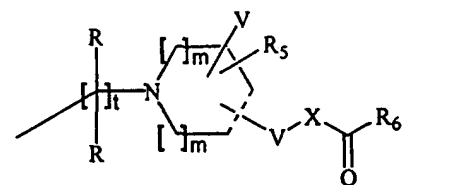
(iii)

20



25

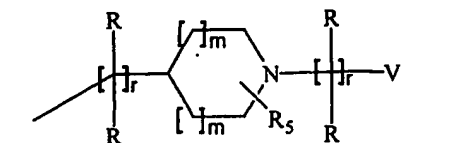
(iv)



30

(v)

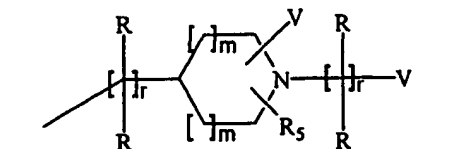
35



40

(vi)

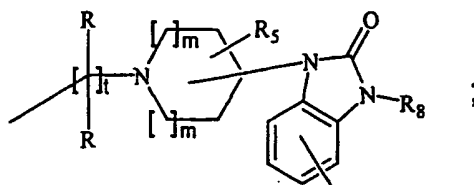
45



-43-

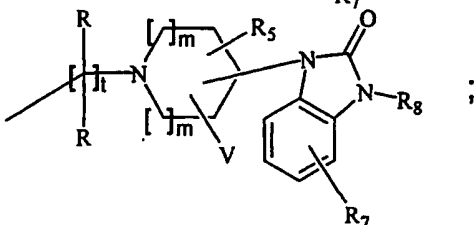
(vii)

5



(viii)

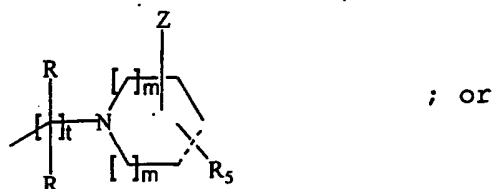
10



15

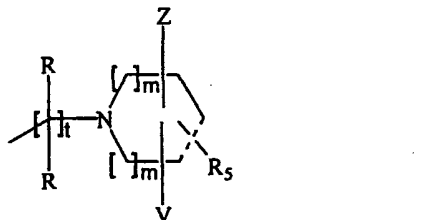
(ix)

20



(x)

25



30

wherein the dashed line represents a single bond or a double bond;

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or -CON(R₃)₂;

40

wherein each V is independently aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or

45

-44-

carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

5

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

20

wherein R₆ is -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

35

wherein R₇ is H; F; Cl; Br; I; -NO₂; -N₃; -CN; straight

-45-

chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; or $-CON(R_3)_2$;

wherein R_8 is independently straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein Z is naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, phthalazinyl, quinoxalinyl, indolyl, benzo[b]furanyl, or benzo[b]thiophenyl; wherein the naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, phthalazinyl, quinoxalinyl, indolyl, benzo[b]furanyl, or benzo[b]thiophenyl may be substituted with one or more F; Cl; Br; I; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C_2 - C_7 alkenyl, C_2 - C_7 alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each m is independently an integer from 0 to 3 inclusive;

wherein each n is independently an integer from 0 to 5 inclusive;

wherein each p is independently an integer from 1 to 7 inclusive;

-46-

wherein q is an integer from 1 to 3 inclusive;

wherein r is an integer from 0 to 3 inclusive;

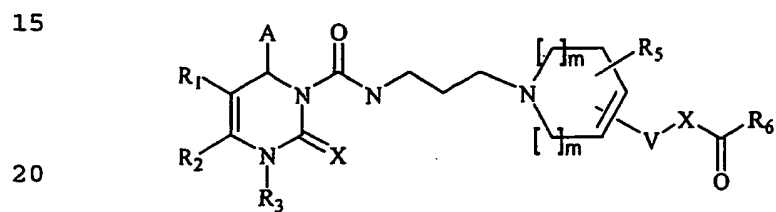
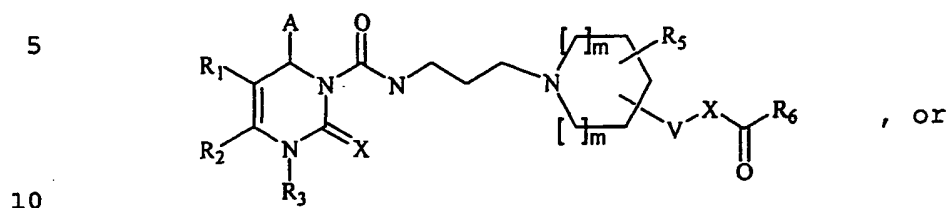
5 wherein t is an integer from 2 to 6 inclusive;

or a pharmaceutically acceptable salt thereof.

10 In one embodiment the compounds of this invention
comprise the (+) enantiomer. In another embodiment, the
compounds comprise the (-) enantiomer.

-47-

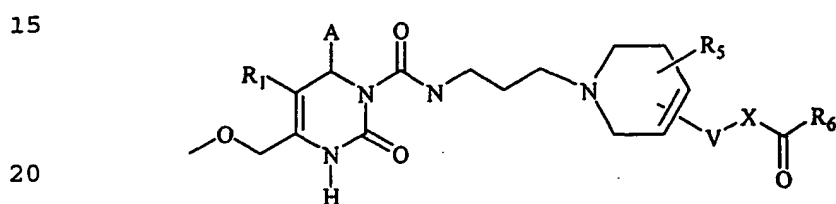
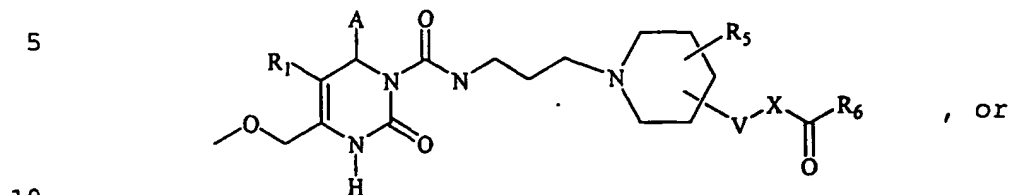
In one embodiment, the compound has the structure:



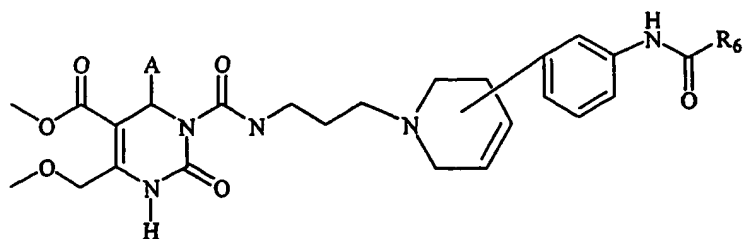
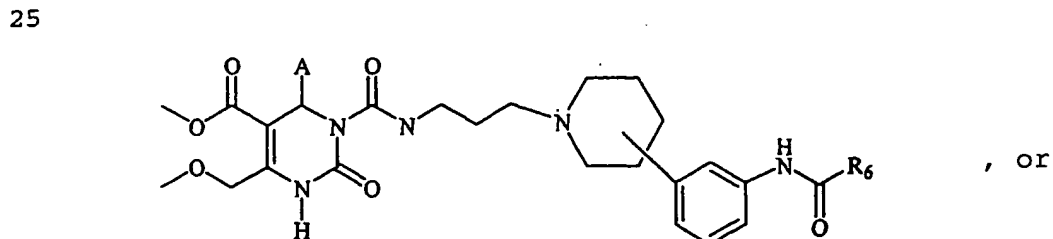
25

-48-

In another embodiment, the compound has the structure:

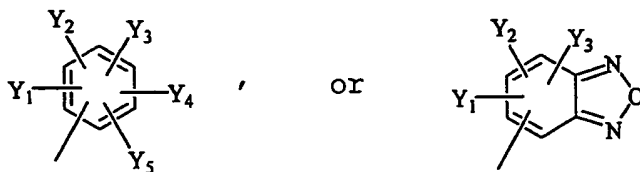


In a further embodiment, the compound has the structure:

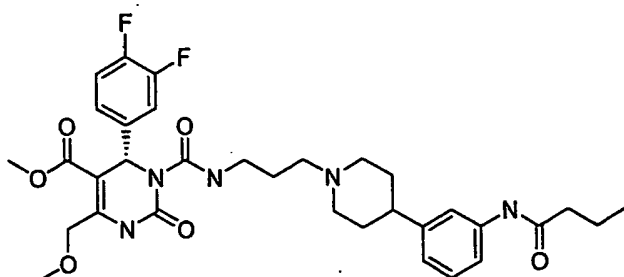
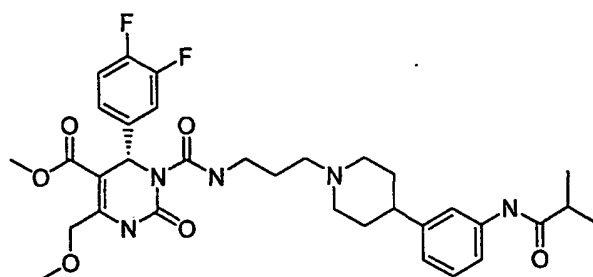
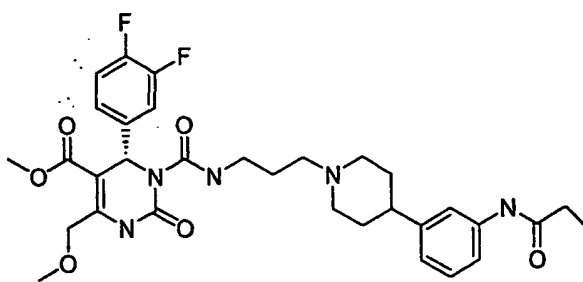


-49-

In yet another embodiment of the present invention variable A is

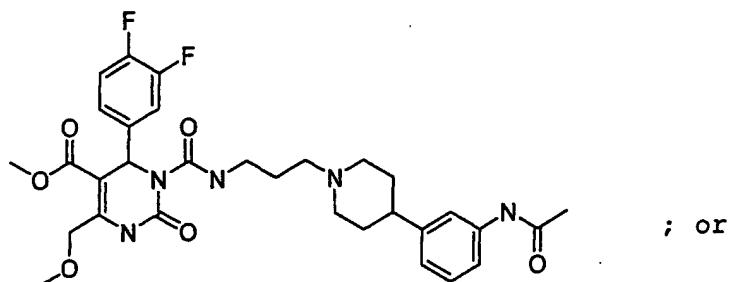


In an embodiment of the present invention, the compound is



-50-

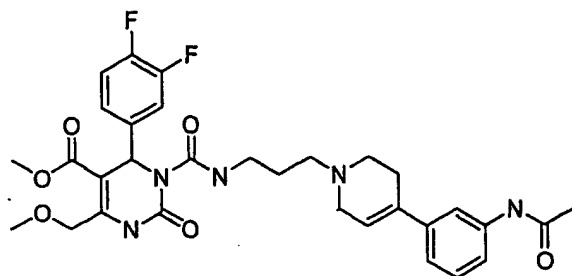
5



10

15

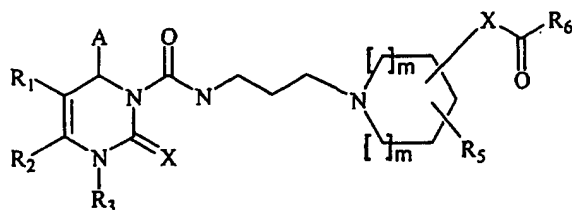
20



25

In another embodiment, the compound has the structure:

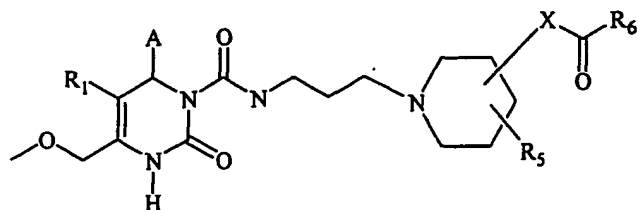
30



35

In further embodiments, the compound has the structure:

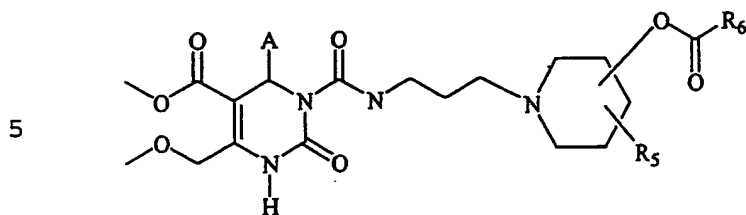
40



45

In an embodiment, the compound has the structure:

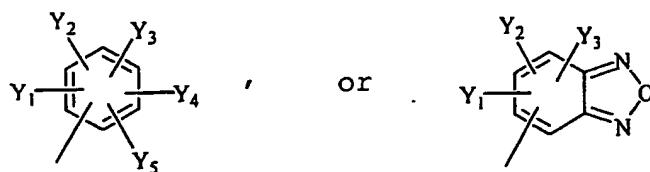
-51-



10

In other embodiments, A is

15

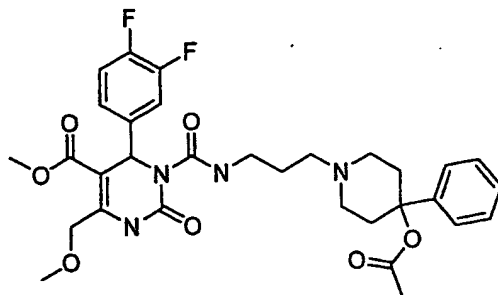


20

In an embodiment of the invention, the compound has the structure:

25

30

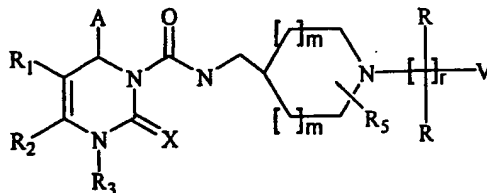


35

In other embodiments, the compound has the structure:

40

45

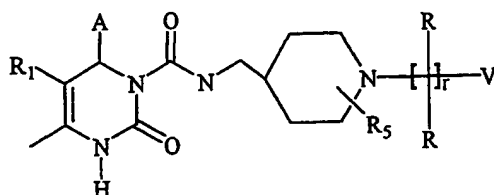


-52-

In additional embodiments, the compound has the structure:

5

10

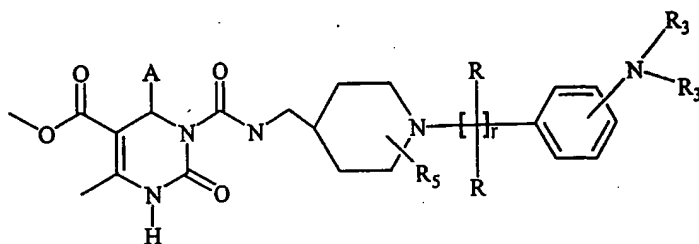


15

In one embodiment of the present invention, the compound has the structure:

20

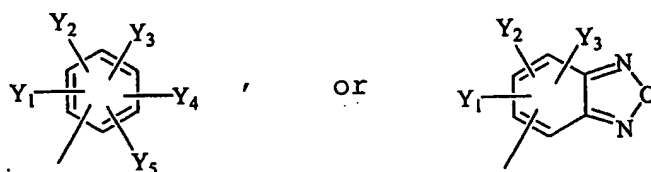
25



In another embodiment of the instant invention, A is

30

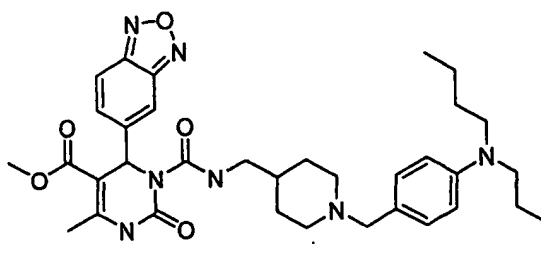
35



In other embodiments of the invention, the compound has the structure:

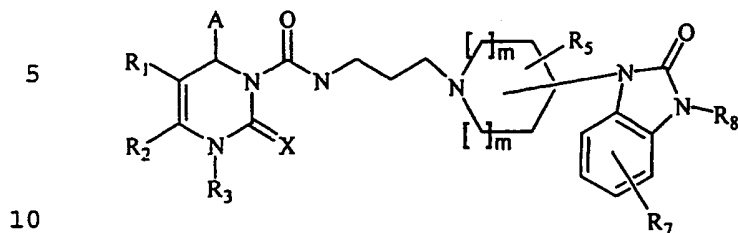
40

45

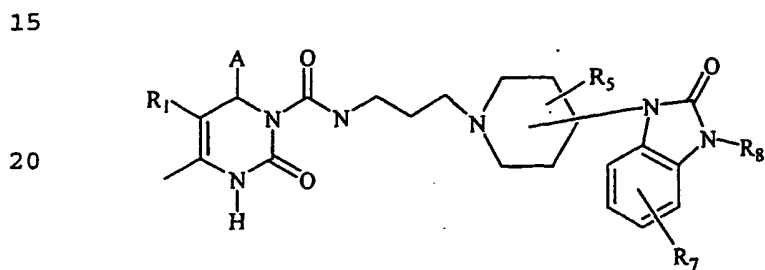


-53-

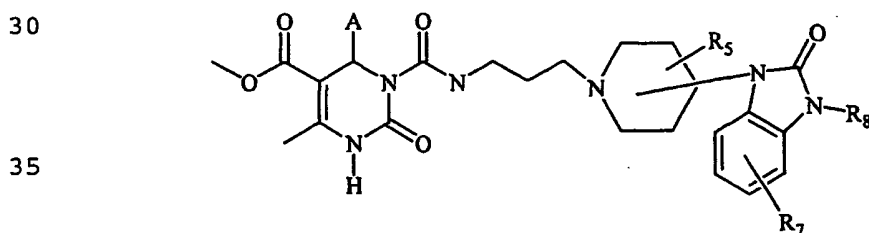
In an embodiment, the compound has the structure:



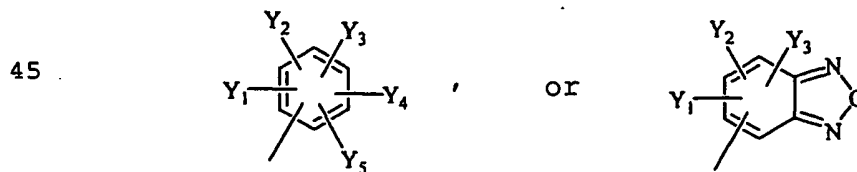
In another embodiment, the compound has the structure:



In yet another embodiment, the compound has the structure:

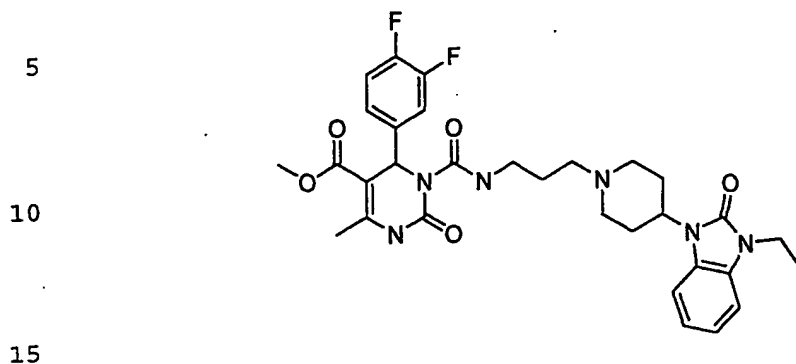


In an embodiment, A is

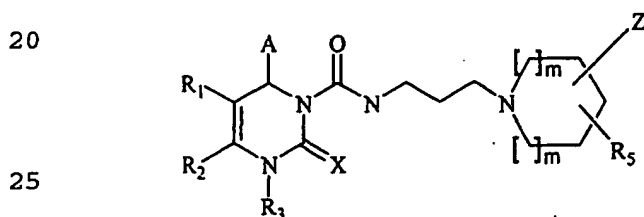


-54-

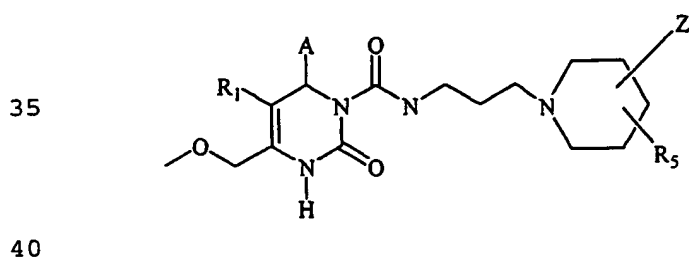
In a further embodiment, the compound has the structure



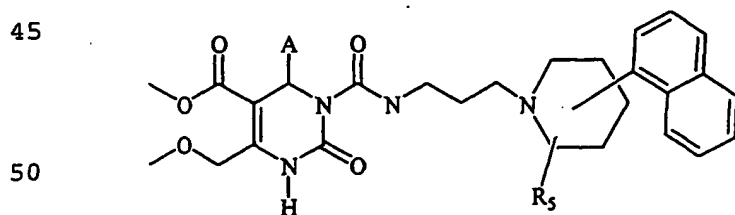
In another embodiment, the compound has the structure:



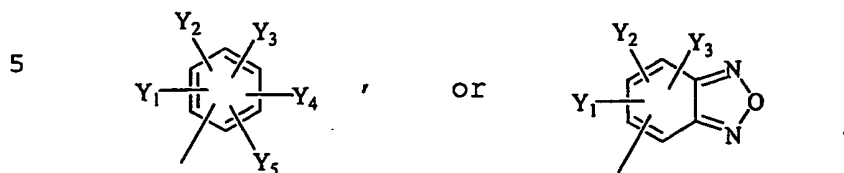
In yet another embodiment, the compound has the structure:



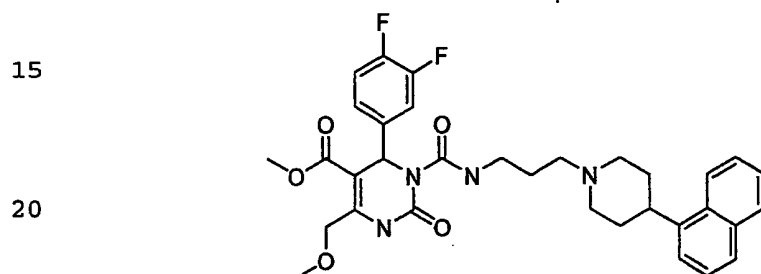
In an additional embodiment, the compound has the structure:



In other embodiments, A is

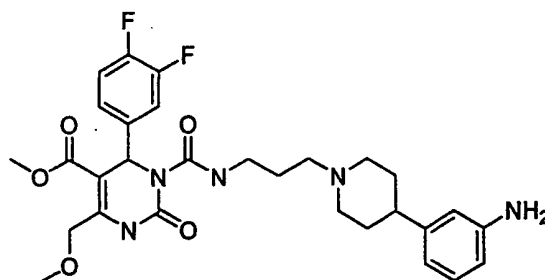


In an embodiment, the compound has the structure:



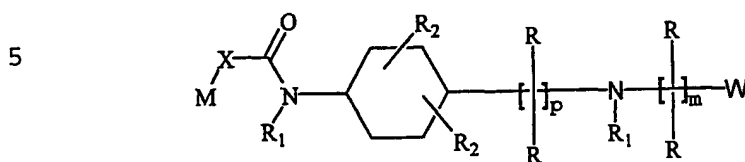
25 In yet another embodiment, the compound is
(+)-1,2,3,6-tetra-hydro-1-{n-[4-(3,-acetamido)-phenyl-
piperidin-1-yl]propyl}carboxamido-4-methoxymethyl-6-(3,4-
difluoro-phenyl)-2-oxopyrimidine-5-carboxylic acid methyl
ester. In a further embodiment, the compound is
30 (-)-1,2,3,6-tetra-hydro-1-{n-[4-(3,-acet-amido)-phenyl-
piperidin-1-yl]propyl}carboxamido-4-methoxymethyl-6-(3,4-
difluoro-phenyl)-2-oxopyrimidine-5-carboxylic acid methyl
ester.

35 In a further embodiment, the compound is:



-56-

In a further embodiment, the compound has the structure:



10 wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -SR₃; -CO₂R₃; or
15 -OR₃;

wherein each R₁ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
20 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

wherein each R₂ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
25 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; or aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃;
30 -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
35 monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R₃ is independently -H; straight chained or

-57-

branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl;

5

wherein M is aryl or heteroaryl, optionally substituted
with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN;
-NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl;
C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

15 wherein X is (CH₂)_n, O, S or NR₃;

wherein W is

(a) C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl optionally
substituted with one or more COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃;
straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl; or

(b) aryl or heteroaryl optionally substituted with one
or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN;
-NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃;
straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl;

35

wherein m is an integer from 0 to 4 inclusive;

-58-

wherein n is an integer from 0 to 6 inclusive;

wherein p is an integer from 1 to 4 inclusive;

5 wherein q is an integer from 1 to 3 inclusive;

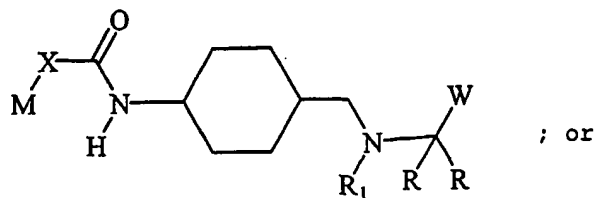
or a pharmaceutically acceptable salt thereof.

10 In one embodiment the compounds of this invention comprise the (+) enantiomer. In another embodiment, the compounds comprise the (-) enantiomer.

In an embodiment, the compound has the structure:

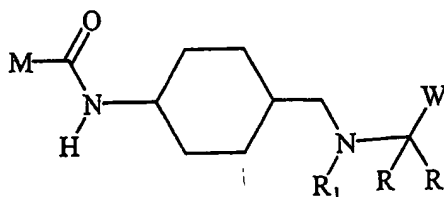
15

20



25

30



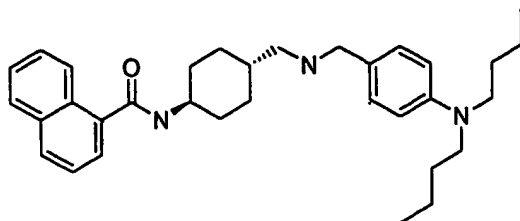
35

In a further embodiment, W is phenyl optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; or (CH₂)_qSR₃.

In another embodiment, the compound has the structure

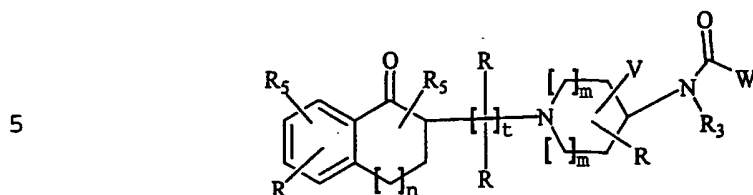
40

45



-59-

In one embodiment, the compound has the structure:



- 10 wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or -CON(R₃)₂;
- 15 wherein each R₁ is independently -H; F; Cl; Br; I; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
- 20 cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
- 25 -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
- 30 cycloalkenyl;

- wherein each R₃ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
- 35 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl

-60-

or cycloalkenyl;

wherein R_5 is -H; -NO₂; -N₃; -CN; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
5 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
-CON(R₃)₂; aryl or heteroaryl, wherein the aryl or
heteroaryl is optionally substituted with one or more F;
10 Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
-SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched
C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl,
or carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
15 monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein V is H; aryl or heteroaryl, optionally
substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃;
20 -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃;
(CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched C₂-C₇
alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
25 monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein W is

30 (a) C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl optionally
substituted with one or more COR₃; CO₂R₃;
-CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
(CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
35 branched C₁-C₇ alkyl, monofluoroalkyl,

-61-

polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or branched
C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl;
or

5

(b) aryl or heteroaryl optionally substituted with
one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃;
(CH₂)_qSR₃; straight chained or branched C₁-C₇
alkyl, monofluoroalkyl, polyfluoroalkyl,
aminoalkyl, or carboxamidoalkyl; straight
chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl;

10

wherein each m is independently an integer from 0 to 3
inclusive;

wherein n is an integer from 0 to 2 inclusive;

20

wherein p is an integer from 1 to 7 inclusive;

wherein q is an integer from 1 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

25

or a pharmaceutically acceptable salt thereof.

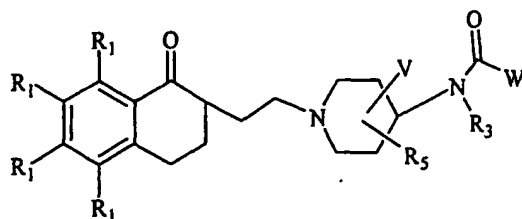
30

In one embodiment the compounds of this invention comprise
the (+) enantiomer. In another embodiment, the compounds
comprise the (-) enantiomer.

In an additional embodiment, the compound has the
structure:

-62-

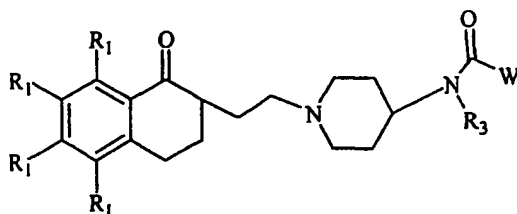
5



10

In a further embodiment, the compound has the structure

15



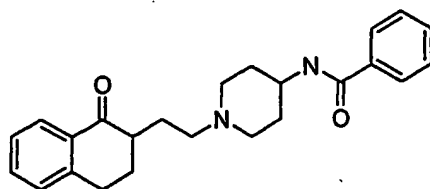
20

In yet another embodiment, W is phenyl optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; or straight chained or branched C₁-C₇ alkyl groups.

25

In yet another embodiment, the compound has the structure

30



35

-63-

In the present invention, the term "aryl" includes phenyl and naphthyl and the term "heteroaryl" is used to include five and six membered unsaturated rings that may contain one or more heteroatoms such as oxygen, sulfur, and nitrogen. Examples of heteroaryl groups include, but are not limited to, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, and triazinyl.

10

In addition the term "heteroaryl" is used to include fused bicyclic ring systems that may contain one or more heteroatoms such as oxygen, sulfur and nitrogen. Examples of such heteroaryl groups include, but are not limited to, indoliziny, indolyl, isoindolyl, benzo[b]furanyl, benzo[b]thiophenyl, indazolyl, benzimidazolyl, benzthiazolyl, purinyl, imidazo[2,1-b]thiazolyl, quinolinyl, isoquinolinyl, quinoliziny, and 2,1,3-benzothiazolyl.

20

Included in this invention are pharmaceutically acceptable salts and complexes of all of the compounds described herein. The salts include but are not limited to the acids and bases listed herein. The salts include, but are not limited to the following inorganic acids: hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid and boric acid. The salts include, but are not limited to the following organic acids: acetic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, maleic acid, citric acid, methanesulfonic acid, benzoic acid, glycolic acid, lactic acid and mandelic acid. The salts include, but are not limited to the inorganic base, ammonia. The salts include, but are not limited to the following organic bases: methylamine, ethylamine, propylamine, dimethylamine, diethylamine, trimethylamine, triethylamine,

35

-64-

ethylenediamine, hydroxyethylamine, morpholine, piperazine and guanidine. This invention further provides for the hydrates and polymorphs of all of the compounds described herein.

5

The present invention includes within its scope prodrugs of the compounds of the invention. In general, such prodrugs will be functional derivatives of the compounds of the invention which are readily convertible in vivo into the required compound. Thus, in the present invention, the term "administering" shall encompass the treatment of the various conditions described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in Design of Prodrugs, ed. H. Bundgaard, Elsevier, 1985.

20

The present invention further includes metabolites of the compounds of the present invention. Metabolites include active species produced upon introduction of compounds of this invention into the biological milieu.

25

This invention further provides a pharmaceutical composition comprising a therapeutically effective amount of the compound of the invention and a pharmaceutically acceptable carrier. In one embodiment, the amount of the compound is an amount from about 0.01 mg to about 800 mg.

30

In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 500 mg. In another embodiment, the amount of the compound is an amount from about 0.01 mg to about 250 mg. In another embodiment, the amount of the compound is an amount from about 0.1 mg to about 60 mg. In another embodiment, the amount of the

35

-65-

compound is an amount from about 1 mg to about 20 mg. In
a further embodiment, the carrier is a liquid and the
composition is a solution. In another embodiment, the
carrier is a solid and the composition is a tablet. In a
5 further embodiment, the carrier is a gel and the
composition is a suppository.

This invention provides a pharmaceutical composition made
by combining a therapeutically effective amount of the
10 compound of this invention and a pharmaceutically
acceptable carrier.

This invention provides a process for making a
pharmaceutical composition comprising combining a
15 therapeutically effective amount of the compound of this
invention and a pharmaceutically acceptable carrier.

In the practice of this invention the "pharmaceutically
acceptable carrier" is any physiological carrier known to
20 those of ordinary skill in the art useful in formulating
pharmaceutical compositions.

In one preferred embodiment the pharmaceutical carrier may
be a liquid and the pharmaceutical composition would be in
25 the form of a solution. In another equally preferred
embodiment, the pharmaceutically acceptable carrier is a
solid and the composition is in the form of a powder or
tablet. In a further embodiment, the pharmaceutical carrier
is a gel and the composition is in the form of a
30 suppository or cream. In a further embodiment the compound
may be formulated as a part of a pharmaceutically
acceptable transdermal patch.

A solid carrier can include one or more substances which
35 may also act as flavoring agents, lubricants, solubilizers,

-66-

suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form

-67-

compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

5

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by for example, intramuscular, intrathecal, epidural, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds may be prepared as a sterile solid composition which may be dissolved or suspended at the time of administration using sterile water, saline, or other appropriate sterile injectable medium. Carriers are intended to include necessary and inert binders, suspending agents, lubricants, flavorants, sweeteners, preservatives, dyes, and coatings.

10

15

The compound can be administered orally in the form of a sterile solution or suspension containing other solutes or suspending agents (for example, enough saline or glucose to make the solution isotonic), bile salts, acacia, gelatin, sorbitan monoleate, polysorbate 80 (oleate esters of sorbitol and its anhydrides copolymerized with ethylene oxide) and the like.

20

25

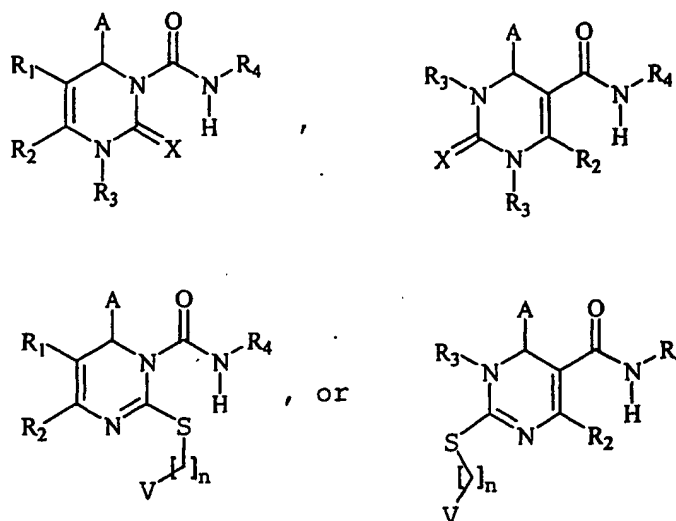
The compound can also be administered orally either in liquid or solid composition form. Compositions suitable for oral administration include solid forms, such as pills, capsules, granules, tablets, and powders, and liquid forms, such as solutions, syrups, elixirs, and suspensions. Forms useful for parenteral administration include sterile solutions, emulsions, and suspensions.

30

-68-

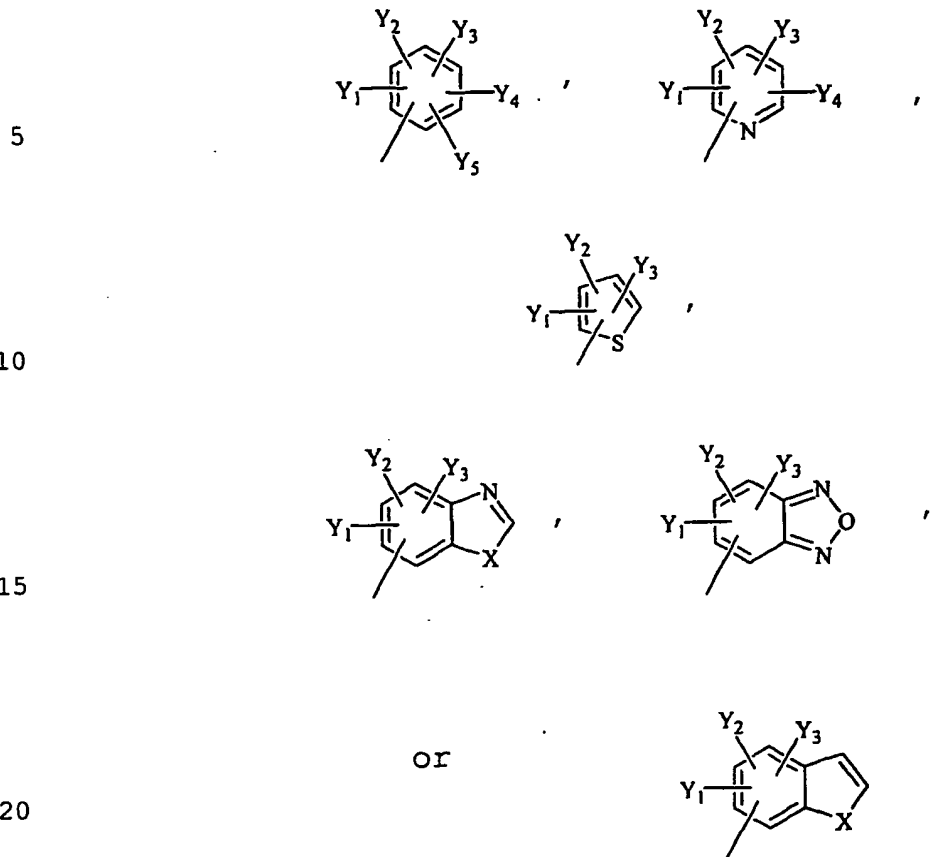
The present invention also provides a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject wherein the compound has the structure:

10



-69-

wherein A is



wherein each of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is independently -H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - NO_2 ; - N_3 ; -CN; - OR_3 , - $OCOR_3$, - COR_3 , - $CON(R_3)_2$, or - $COOR_3$; or any two of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 present on adjacent carbon atoms can constitute a methylenedioxy group;

wherein each X is independently S; O; or NR_3 ;

wherein R_1 is -H; - NO_2 ; -CN; straight chained or branched

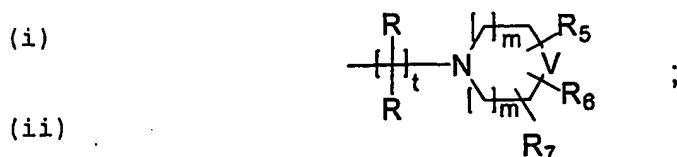
-70-

C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight
 chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
 5 -CON(R₃)₂; or CO₂(CH₂)_nV;

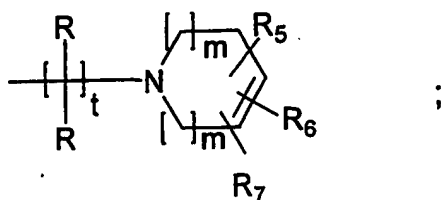
wherein R₂ is -H; straight chained or branched C₁-C₇
 alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl,
 monofluoroalkyl or polyfluoroalkyl; straight chained or
 10 branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀
 cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-
 15 C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃,
 -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃,
 -CH₂X(CH₂)_pNHCXR₅; -OR₃; or R₁ and R₂ together form a
 lactone ring;

wherein each R₃ is independently -H; straight chained or
 20 branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-
 C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
 or cycloalkenyl;

25 wherein R₄ is



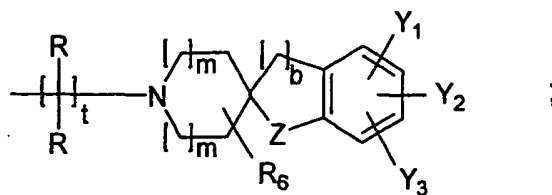
30



-71-

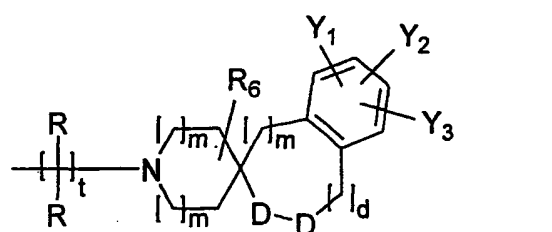
(iii)

5



(iv)

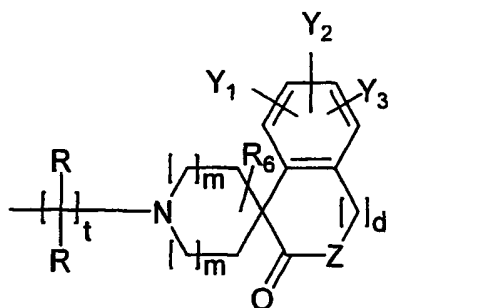
10



15

(v)

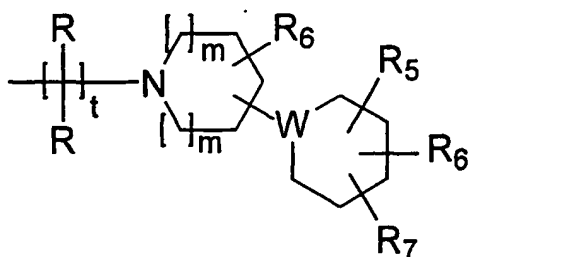
20



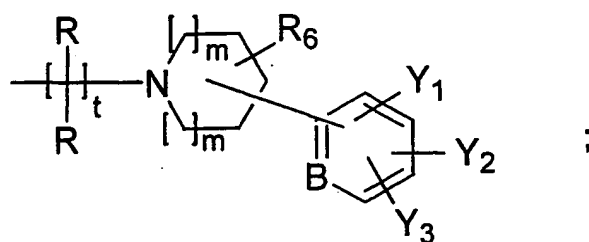
25

-72-

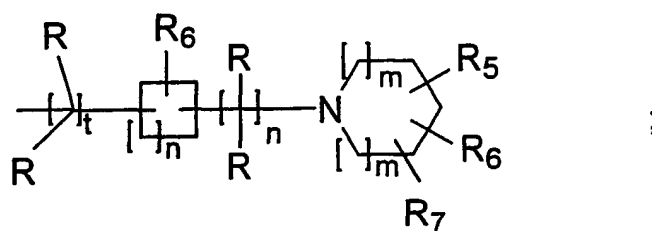
(vi)



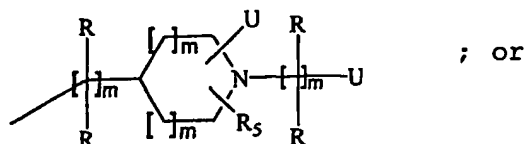
(vii)



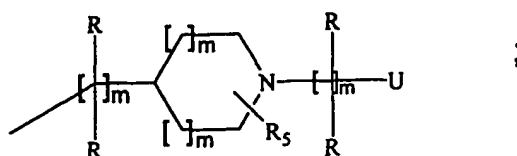
(viii)



(ix)



(x)



-73-

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or
5 -CN(R₃)₂;

wherein B is N or CY₄;

wherein each D is independently C(R₃)₂; O; S; NR₃; CO; or
10 CS;

wherein each U is independently aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
15 (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
20 cycloalkenyl;

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

wherein W is CR₅; CR₆ or N;
25

wherein Z is S; O; C(R₃)₂; or NR₃;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
30 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or
35 more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;

-74-

5 $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; $-XCOR_8$; straight
chained or branched C_1-C_7 alkyl, monofluoroalkyl,
polyfluoroalkyl, or aminoalkyl; straight chained or
branched C_2-C_7 alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

10 wherein each R_6 is independently $-H$; straight chained or
branched C_1-C_7 alkyl, hydroxyalkyl, aminoalkyl,
alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$;
or $-CON(R_3)_2$;

15 wherein R_7 is $-H$; aryl or heteroaryl, optionally
substituted with one or more F ; Cl ; Br ; I ; COR_3 ; CO_2R_3 ;
 $-CON(R_3)_2$; CN ; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$;
 $(CH_2)_qSR_3$; $-XCOR_8$; straight chained or branched C_1-C_7
20 alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
straight chained or branched C_2-C_7 alkenyl, C_2-C_7 alkynyl;
 C_3-C_7 cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

25 wherein R_8 is $-H$; straight chained or branched C_1-C_7
alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; or
30 $-CON(R_3)_2$; aryl or heteroaryl, optionally substituted with
one or more F ; Cl ; Br ; I ; COR_3 ; CO_2R_3 ; $-CON(R_3)_2$; CN ; $-NO_2$;
 $-N(R_3)_2$; $-OR_3$; $-SR_3$; $(CH_2)_qOR_3$; $(CH_2)_qSR_3$; straight chained
or branched C_1-C_7 alkyl, monofluoroalkyl, polyfluoroalkyl,
aminoalkyl, or carboxamidoalkyl; straight chained or
35 branched C_2-C_7 alkenyl, C_2-C_7 alkynyl; C_3-C_7 cycloalkyl,

-75-

monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein b is 1 or 2;

5

wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to 3 inclusive;

10

wherein each n is independently an integer from 0 to 5 inclusive;

15

wherein each p is independently an integer from 1 to 7 inclusive;

wherein q is an integer from 1 to 3 inclusive;

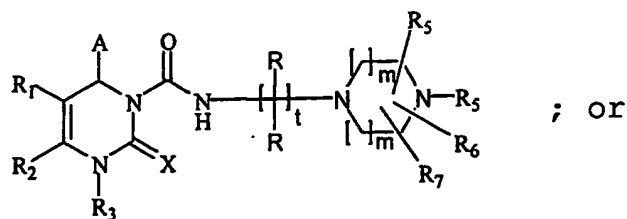
wherein t is an integer from 2 to 6 inclusive;

20

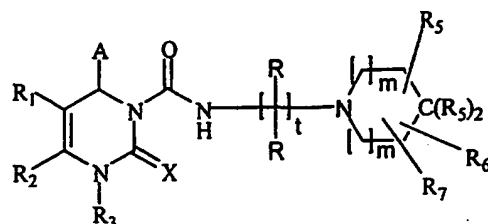
or a pharmaceutically acceptable salt thereof.

In one embodiment, the compound has the structure

25



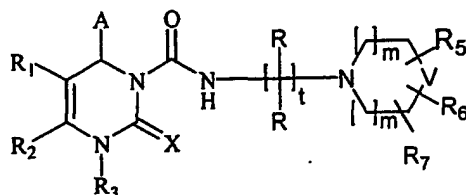
30



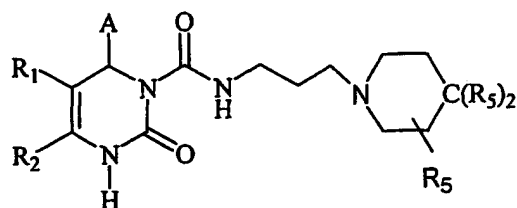
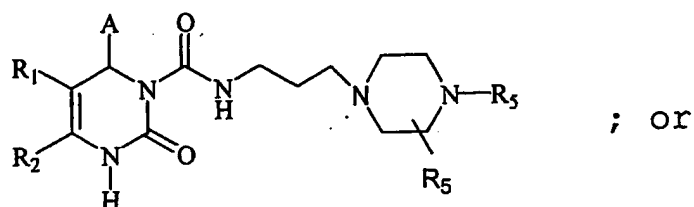
35

-76-

In a further embodiment, the compound has the structure



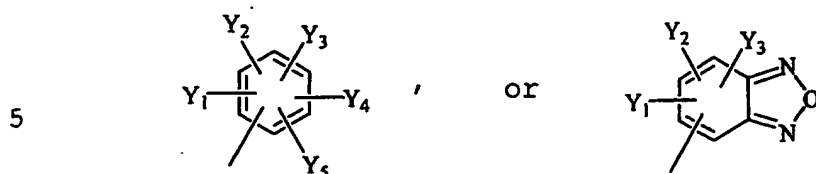
In an additional embodiment, the compound has the structure



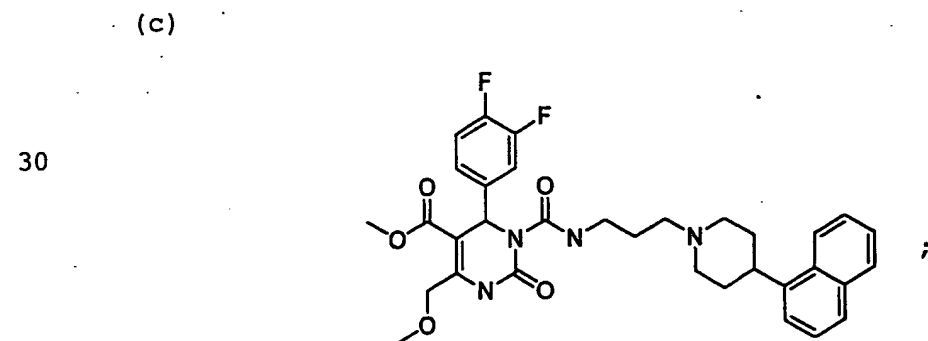
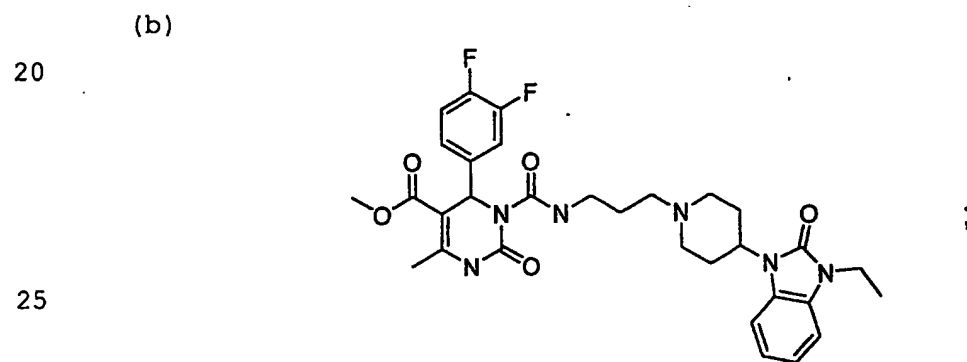
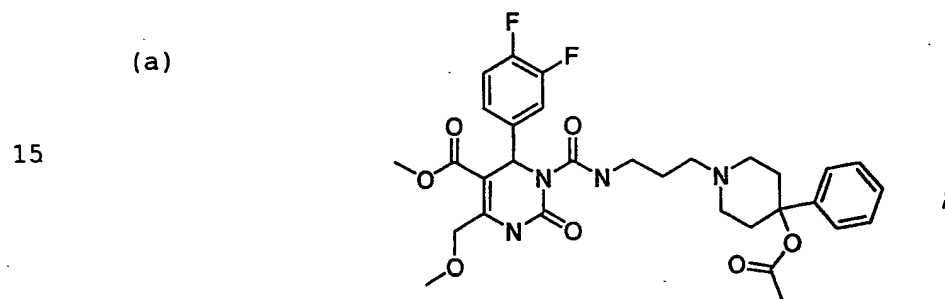
In a further embodiment, at least one R_5 group is an aryl or heteroaryl group optionally substituted with one or more F; Cl; Br; I; $-NO_2$; $-N(R_3)_2$; $-OR_3$; $-XCOR_8$; or straight chained or branched C_1 - C_7 alkyl.

-77-

In another embodiment, A is:



10 In further embodiments, the compound is selected from the group consisting of:

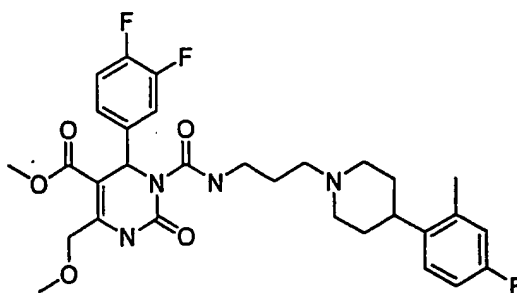


35

-78-

(d)

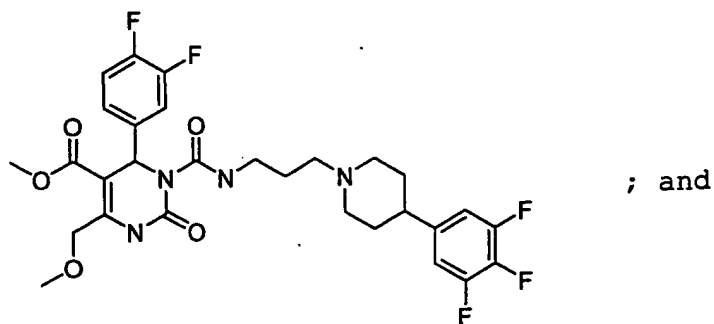
5



(e)

10

15

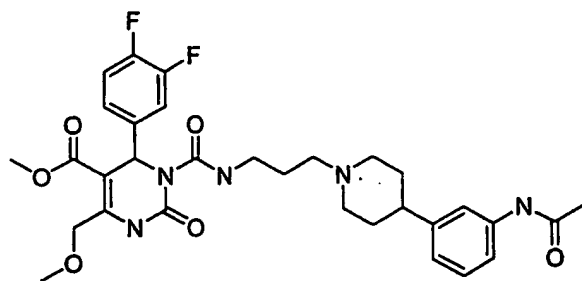


; and

20

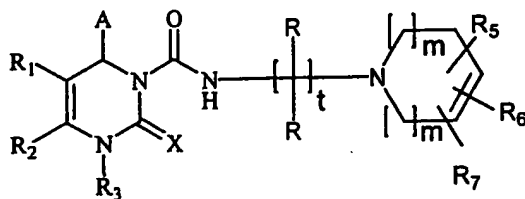
(f)

25



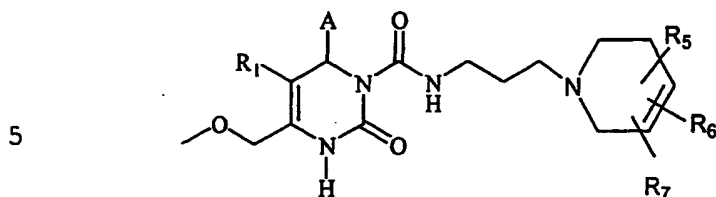
In other embodiments, the compound has the structure

30



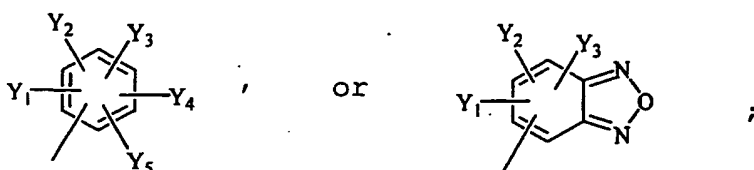
-79-

In a further embodiment, the compound has the structure



In additional embodiments, A is

10



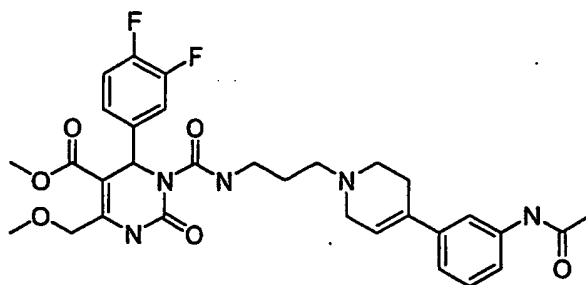
15

and R₇ is phenyl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; or straight chained or branched C₁-C₇ alkyl.

20

In one embodiment, the compound has the structure

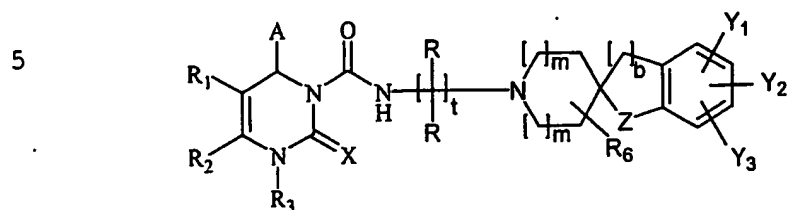
25



30

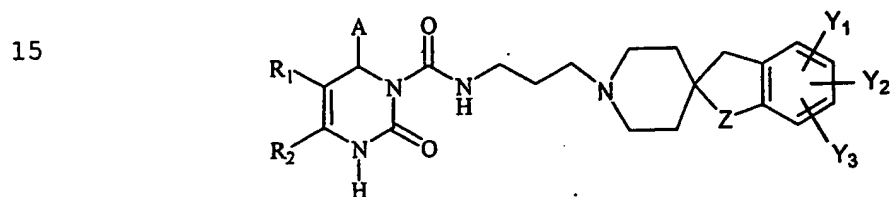
-80-

In an embodiment of the present invention, the compound has the structure



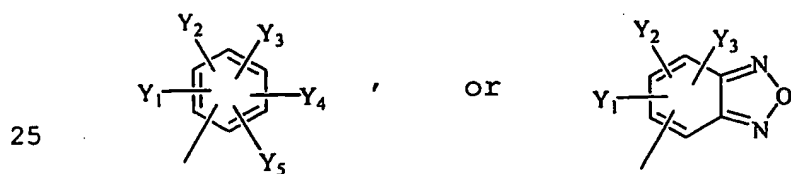
10

In yet another embodiment, the compound has the structure



20

In further embodiments, A is



and Z is O or CH₂.

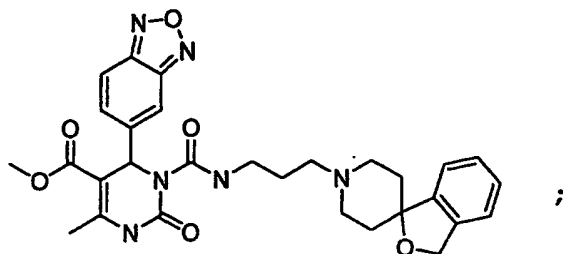
30

-81-

In an additional embodiment, the compound is selected from the group consisting of

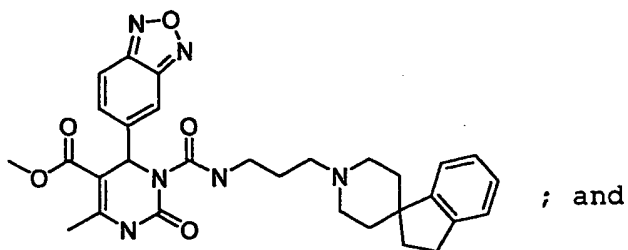
5

10



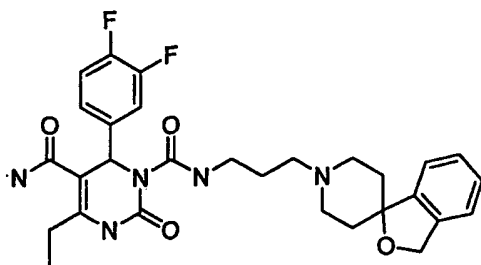
15

20



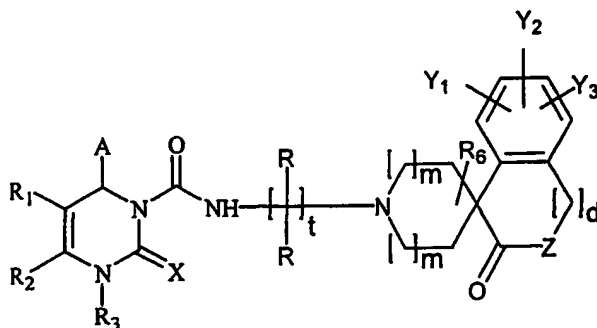
25

30

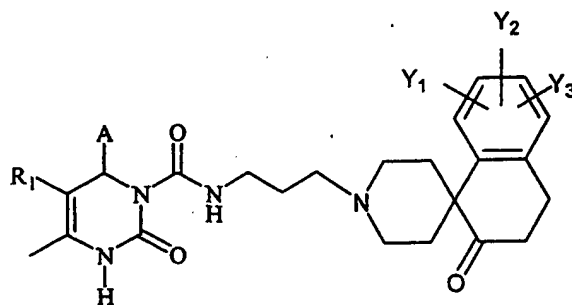


-82-

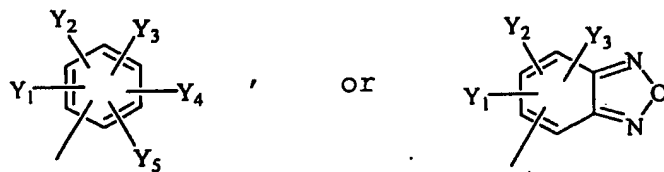
In one embodiment, the compound has the structure



In a further embodiment, the compound has the structure

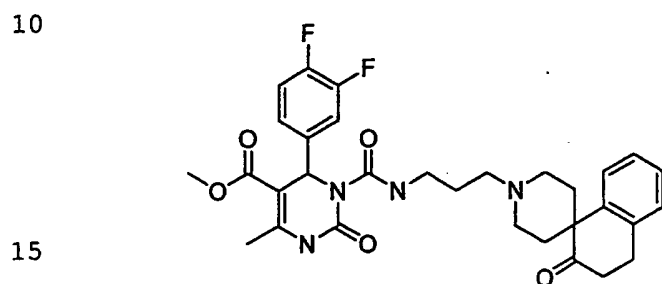
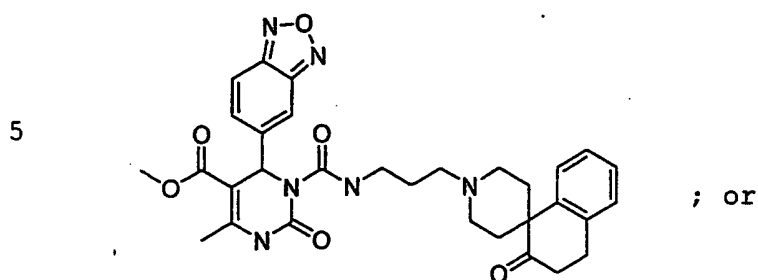


In another embodiment, A is

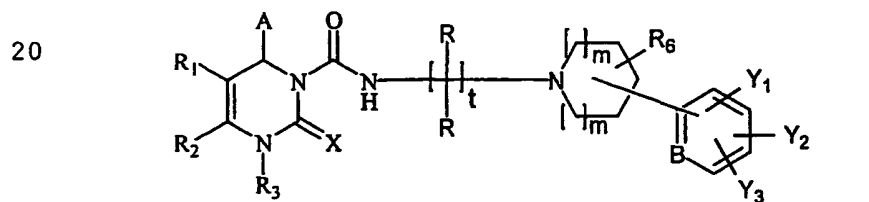


-83-

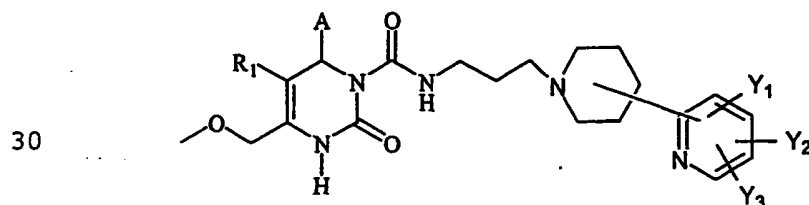
In yet another embodiment, the compound is



In a further embodiment, the compound has the structure

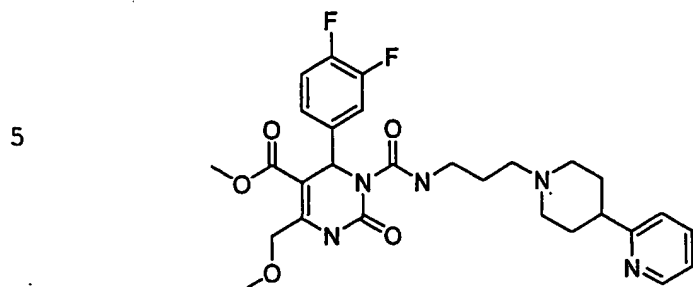


25 In another embodiment, the compound has the structure

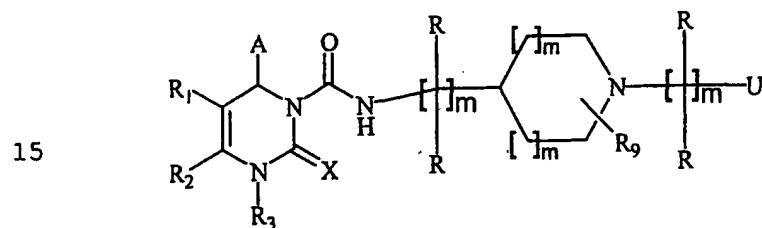


-84-

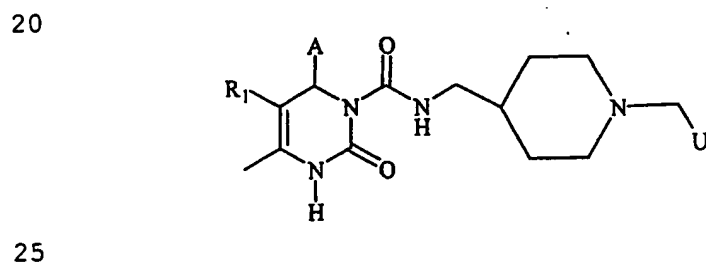
In yet another embodiment, the compound has the structure



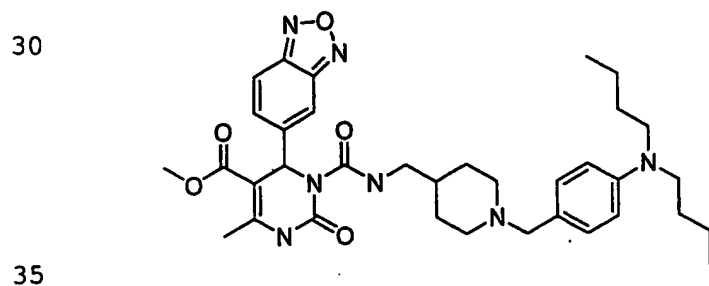
10 In one embodiment, the compound has the structure



20 In another embodiment, the compound has the structure

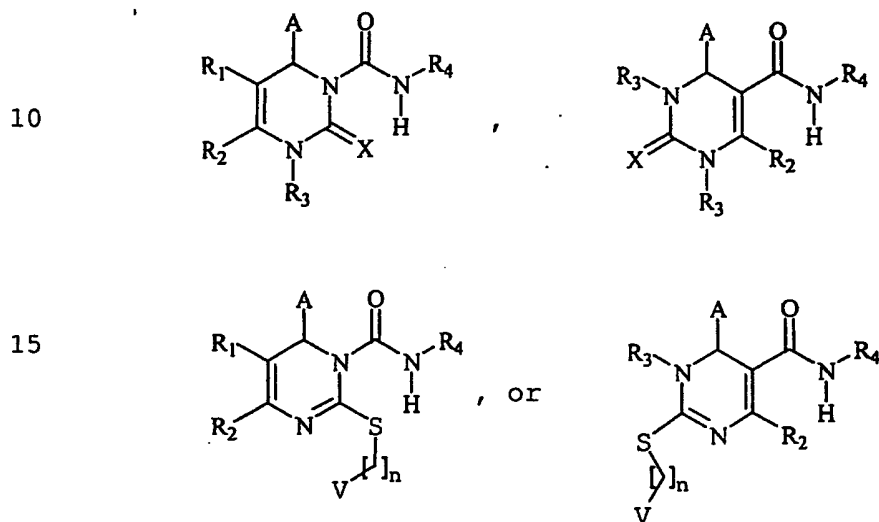


30 In another embodiment, the compound has the structure



-85-

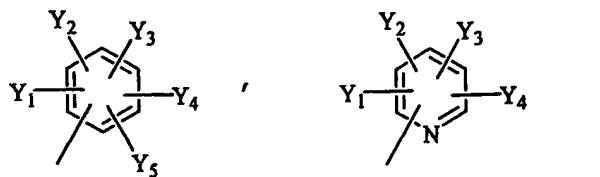
This invention further provides a method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound effective to reduce the body mass of the subject wherein the compound has the structure:



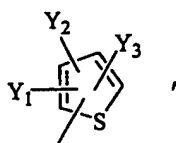
-86-

wherein A is

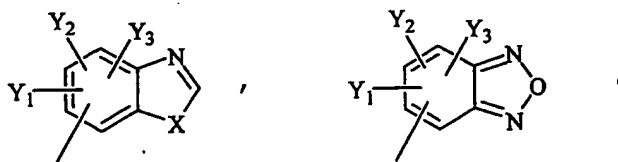
5



10

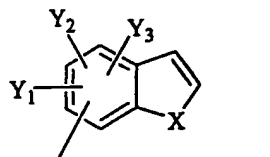


15



20

or



wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H;
 25 straight chained or branched C₁-C₇ alkyl, monofluoroalkyl
 or polyfluoroalkyl; straight chained or branched C₂-C₇
 alkenyl or alkynyl; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl; -F, -Cl, -Br, or -I;
 30 -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CON(R₃)₂, or -COOR₃;
 or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent
 carbon atoms can constitute a methylenedioxy group;

wherein each X is independently S; O; or NR₃;

35

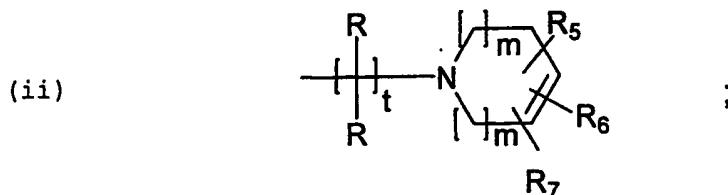
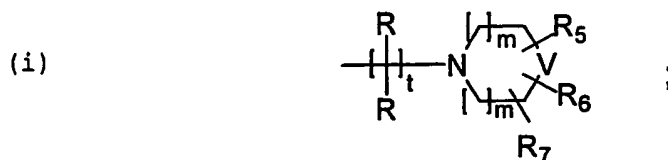
-87-

wherein R_1 is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; or CO₂(CH₂)_nV;

wherein R_2 is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, -CH₂X(CH₂)_pNHCXR₅; -OR₃; or wherein R_1 and R_2 together form a lactone ring;

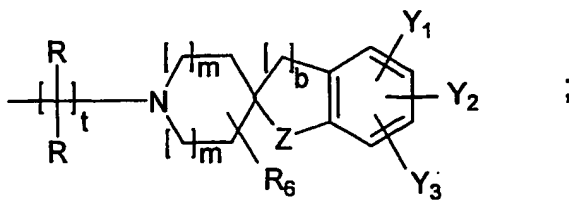
wherein each R_3 is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_4 is



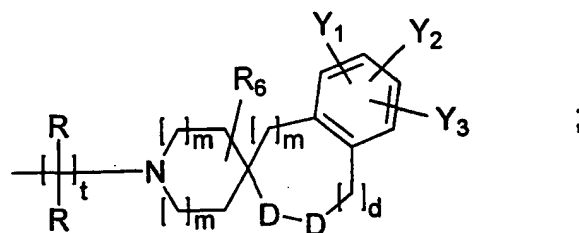
-88-

(iii)



5

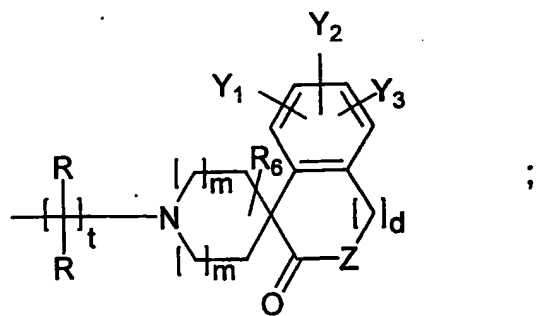
(iv)



10

15

(v)

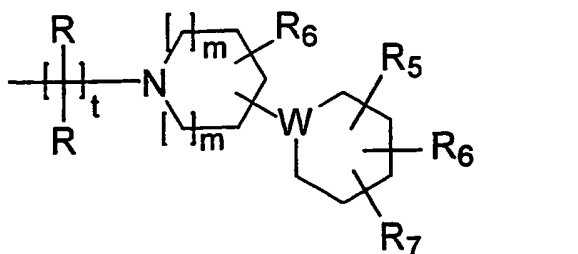


20

25

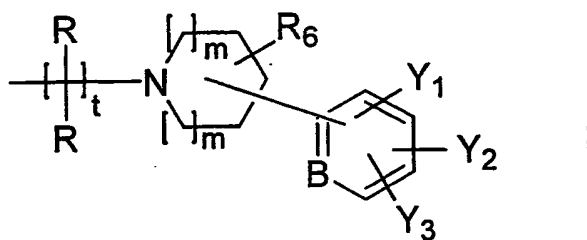
(vi)

5



(vii)

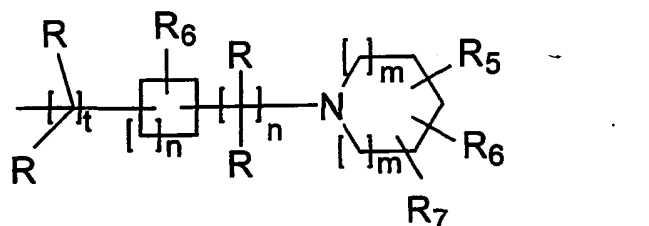
10



15

(viii)

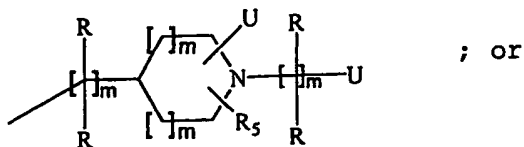
20



25

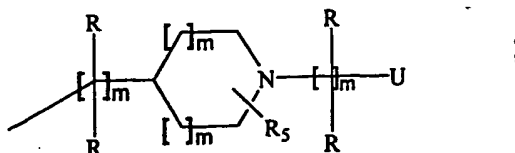
(ix)

30



35

(x)



-90-

wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or
5 -CN(R₃)₂;

wherein B is N or CY₄;

wherein each D is independently C(R₃)₂; O; S; NR₃; CO; or
10 CS;

wherein each U is independently aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
15 (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
20 cycloalkenyl;

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

wherein W is CR₅; CR₆ or N;
25

wherein Z is S; O; C(R₃)₂; or NR₃;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl;
30 straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or
35 more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;

-91-

-N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight
 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
 polyfluoroalkyl, or aminoalkyl; straight chained or
 branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
 5 monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl;

wherein each R₆ is independently -H; straight chained or
 branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl,
 10 monofluoroalkyl or polyfluoroalkyl; straight chained or
 branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl,
 monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;
 -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or
 -CON(R₃)₂;

15 wherein R₇ is -H; aryl or heteroaryl, optionally
 substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃;
 -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃;
 (CH₂)_qSR₃; -XCOR₈; straight chained or branched C₁-C₇
 20 alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
 straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl;
 C₃-C₇ cycloalkyl, monofluorocycloalkyl,
 polyfluorocycloalkyl or cycloalkenyl;

25 wherein R₈ is -H; straight chained or branched C₁-C₇
 alkyl, monofluoroalkyl or polyfluoroalkyl; straight
 chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
 cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or
 30 -CON(R₃)₂; aryl or heteroaryl, optionally substituted with
 one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
 -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained
 or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl,
 aminoalkyl, or carboxamidoalkyl; straight chained or
 35 branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,

-92-

monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein b is 1 or 2;

5

wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to 3
inclusive;

10

wherein each n is independently an integer from 0 to 5
inclusive;

15

wherein each p is independently an integer from 1 to 7
inclusive;

wherein q is an integer from 1 to 3 inclusive;

20

wherein t is an integer from 2 to 6 inclusive;

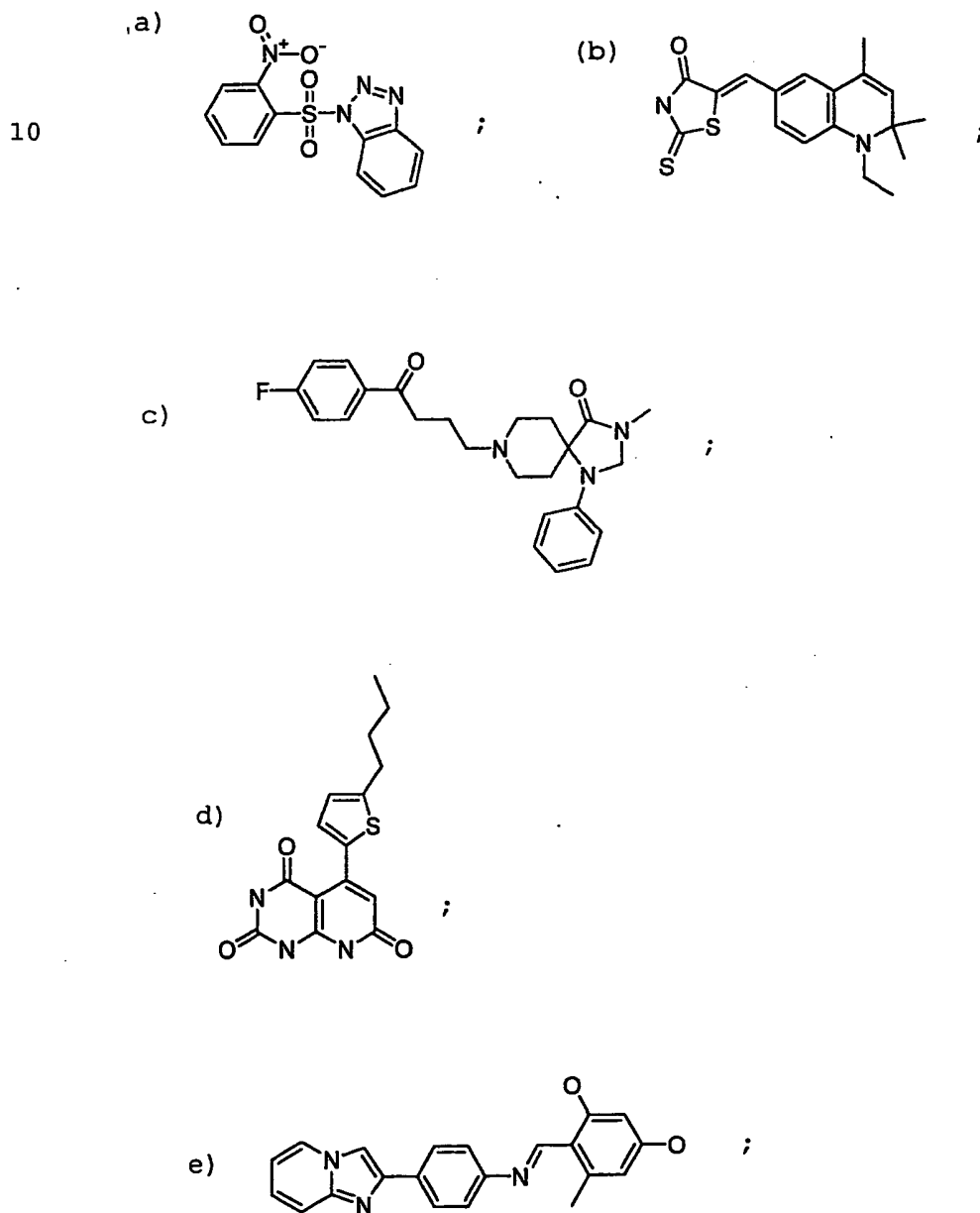
or a pharmaceutically acceptable salt thereof.

25

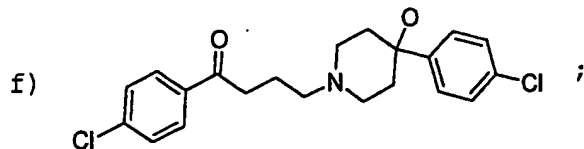
In addition, the present invention provides a method of
treating a subject suffering from depression and/or anxiety
which comprises administering to the subject a compound of
the aforementioned formula in an amount effective to treat
the subject's depression and/or anxiety.

-93-

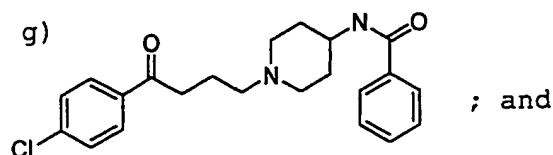
This invention also provides a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject wherein the compound is selected from the group consisting of:



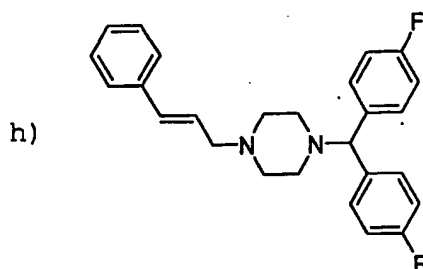
-94-



5



10



15

20

This invention further provides a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound of the present invention effective to decrease the consumption of food by the subject.

25

This invention also provides a method of treating a feeding disorder in a subject which comprises administering to the subject an amount of a compound of the present invention effective to decrease the consumption of food by the subject. In an embodiment of the present invention, the feeding disorder is bulimia, obesity or bulimia nervosa. In a further embodiment, the subject is a vertebrate, a mammal, a human or a canine. In yet another embodiment, the compound is administered in combination with food.

30
35

-95-

In the subject invention a "therapeutically effective amount" is any amount of a compound which, when administered to a subject suffering from a disease against which the compounds are effective, causes reduction, remission, or regression of the disease.

One skilled in the art will readily appreciate that appropriate biological assays will be used to determine the therapeutic potential of the claimed compounds for treating the above noted disorders.

Optimal dosages to be administered may be determined by those skilled in the art, and will vary with the particular compound in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular subject being treated will result in a need to adjust dosages, including subject age, weight, gender, diet, and time of administration.

This invention further provides compositions which need not be pharmaceutical as that term is understood in the art. Such compositions comprise a compound in accordance with the subject invention in an amount effective to antagonize an MCH1 receptor and a suitable carrier.

Still further, the invention provides a method of agonizing and/or antagonizing an MCH1 receptor which comprises contacting the receptor, e.g. *in vitro* or *in vivo*, with an amount of a compound of this invention effective to agonize and/or antagonize the receptor.

This invention will be better understood from the Experimental Details which follow. However, one skilled in

-96-

the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

-97-

Experimental Section**I. Synthetic Methods for Examples**

General Methods: All reactions (except for those done by
5 parallel synthesis reaction arrays) were performed under an
Argon atmosphere and the reagents, neat or in appropriate
solvents, were transferred to the reaction vessel via
syringe and cannula techniques. The parallel synthesis
10 reaction arrays were performed in vials (without an inert
atmosphere) using J-KEM heating shakers (Saint Louis, MO).
Anhydrous solvents were purchased from Aldrich Chemical
Company and used as received. The examples described in the
patent (1-37) were named using ACD/Name program (version
2.51, Advanced Chemistry Development Inc., Toronto,
15 Ontario, M5H2L3, Canada). Unless otherwise noted, the ¹H
and ¹³C NMR spectra were recorded at 300 and 75 MHz (QE
Plus) with CDCl₃ as solvent and tetramethylsilane as
internal standard. s = singlet; d = doublet; t = triplet;
q = quartet; p = pentet; sextet; septet; br = broad; m =
20 multiplet. Elemental analyses were performed by Robertson
Microlit Laboratories, Inc. Unless otherwise noted, mass
spectra were obtained using low-resolution electrospray
(ESMS) and MH⁺ is reported. Thin-layer chromatography (TLC)
was carried out on glass plates precoated with silica gel
25 60 F254 (0.25 mm, EM Separations Tech.). Preparative
thin-layer chromatography was carried out on glass sheets
precoated with silica gel GF (2 mm, Analtech). Flash
column chromatography was performed on Merck silica gel 60
(230 - 400 mesh). Melting points (mp) were determined in
30 open capillary tubes on a Mel-Temp apparatus and are
uncorrected.

Procedures for the Synthesis of the Dihydropyrimidine
Intermediates

-98-

5-METHOXYCARBONYL-4-METHOXYMETHYL-1,2,3,6-TETRAHYDRO-2-
OXO-6- (3,4-DIFLUOROPHENYL)-PYRIMIDINE: To a stirring
mixture of methyl 4-methoxyacetoacetate (50.0 g, 0.342
mol), 3,4-difluorobenz-aldehyde (51.4 g, 0.362 mol), and
5 urea (31.6 g, 0.527 mole) in THF (300 mL) at room
temperature were added copper(I) oxide (5.06 g, 0.035 mole)
and acetic acid (2.05 mL), sequentially, followed by
dropwise addition of boron trifluoride diethyl etherate
(56.0 mL, 0.442 mole). The mixture was stirred and
10 refluxed for 8 h, whereupon TLC (1/1 EtOAc/hexanes)
analysis indicated completion of the reaction. The reaction
mixture was cooled and poured into a mixture of ice and
sodium bicarbonate (100 g) and the resulting mixture was
filtered through Celite. The Celite pad was washed with
15 dichloromethane (400 mL). The organic layer was separated
from the filtrate and the aqueous layer was extracted with
more dichloromethane (3 X 300 mL). The combined organic
extracts were dried (sodium sulfate) and the solvent
evaporated. The crude product was purified by flash column
20 (ethyl acetate/hexanes, 1/1; then ethyl acetate), giving
the product as pale yellow foam, which on trituration with
hexane became white powder (103 g, 97%). ¹H NMR d 3.48 (s,
3H), 3.65 (s, 3H), 4.65 (s, 2H), 5.39 (s, 1H), 6.60 (br s,
1H, NH), 7.00 - 7.20 (m, 3H), 7.72 (br s, 1H, NH).

25.

(+)-5-METHOXYCARBONYL-4-METHOXYMETHYL-1,2,3,6-TETRAHYDRO-2-
OXO-6-(3,4-DIFLUOROPHENYL)-PYRIMIDINE: The racemic
intermediate 5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-
30 tetrahydro-2-oxo-6- (3,4-difluorophenyl)pyrimidine was
resolved by chiral HPLC. [Chiralcel OD 20 X 250 mm
#369-703-30604; lambda 254 nm; hexanes/ethanol 90/10; 85 mg
per injection; retention time of the desired enantiomer:
16.94 min., the first enantiomer peak to elute], giving
35 (+) - 5 - methoxycarbonyl - 4 - methoxymethyl -

-99-

1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-pyrimidine (40-42 wt% isolation of the desired enantiomer from the racemate); $[\alpha]_D = + 83.8$ ($c = 0.5$, chloroform). The (-)-isomer was also isolated as the later eluting fraction from the chiral chromatography column.

(+)-5-METHOXYCARBONYL-4-METHOXYMETHYL-1,2,3,6-TETRAHYDRO-2-OXO- 6-(3,4-DIFLUOROPHENYL)-1-[(4-NITROPHENYLOXY) CARBONYL]PYRIMIDINE: To a solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4- difluorophenyl)-pyrimidine (1.98 g, 6.34 mmol) in anhydrous THF (20 mL) at -78 °C under argon atmosphere, a solution of lithium hexamethyldisilazide in THF (1M, 18.0 mL, 18.0 mmol) was added over 2-3 min. and the mixture was stirred for 10 min. This solution was added over 6 min., via a cannula, to a stirred solution of 4-nitrophenyl chloroformate (4.47 g, 22.2 mmol) in THF (20 mL) at -78 °C. Stirring was continued for 10 min. and the mixture was poured onto ice (50 g) and extracted with chloroform (2 X 50 mL). The combined extracts were dried (sodium sulfate) and the solvent was evaporated. The residue was purified by flash column chromatography (hexanes/ethyl acetate, 4/1 to 3.5/1) as the eluent. The product was obtained as yellow syrup which upon trituration with hexanes became a white powder (2.40 g, 79%): ^1H NMR δ 3.52 (s, 3H), 3.74 (s, 3H), 4.65-4.80 (q, $J=16.5$ Hz, 2H), 6.32 (s, 1H), 7.10-7.30 (m, 4H), 7.36 (d, $J=9$ Hz, 2H), 8.27 (d, $J=9$ Hz, 2H).

BENZYL 3-[(3,4-DIFLUOROPHENYL)METHYLENE]-4-OXOPENTANOATE: A solution of benzyl propionylacetate (36.3 g, 176 mmol), 3,4- difluorobenzaldehyde (25.0 g, 176 mmol), piperidine (0.86 mL, 9.0 mmol) and acetic acid (0.49 mL, 9.0 mmol) was refluxed with removal of water using a Dean-Stark apparatus

-100-

for 5 h. The solvent was removed in vacuo and the residue was dissolved in EtOAc. The reaction mixture was washed with water (100 mL), followed by brine (100 mL) and dried over anhydrous Na₂SO₄. The solvent was evaporated, giving a pale yellow syrup (60.2 g). The product was used in the next step without further purification.

5-(BENZYLOXYCARBONYL)-1,6-DIHYDRO-2-METHOXY-4-ETHYL-6-(3,4-DI-FLUOROPHENYL)PYRIMIDINE: A suspension of benzyl 3-[(3,4-di-fluorophenyl)methylene]-4-oxopentanoate (16.0 g, 48.0 mmol), O-methylisourea hydrogen sulfate (16.7 g, 97.0 mmol) and NaHCO₃ (16.3 g, 130 mmol) in DMF (190 mL) was stirred at 70 °C for 20 h. After cooling to room temperature, the mixture was filtered and the filtrate was diluted with EtOAc (300 mL) and then washed with water (4X100 mL), brine (200 mL) and dried over Na₂SO₄. After removal of solvent, the residue was purified by column chromatography (EtOAc/Hexane, 1/9 to 3/7), giving the title compound as a colorless oil (10.6 g, 58%). The NMR analysis showed it to be a mixture of amine/imine tautomers and was used as is in the next step.

5-(BENZYLOXYCARBONYL)-4-ETHYL-1,6-DIHYDRO-2-METHOXY-6-(3,4-DI-FLUOROPHENYL)-1-[(4-NITROPHENYLOXY)CARBONYL]PYRIMIDINE: To a stirring solution of 5-(benzyloxycarbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophenyl)pyrimidine (17.0 g, 44.0 mmol) and 4-dimethylaminopyridine (7.00 g, 57.3 mmol) in CH₂Cl₂ (200 mL) was added 4-nitrophenyl chloroformate as a powder (11.5 g, 57.1 mmol) at room temperature. The reaction mixture was stirred for 12 h and then the solvent was removed in vacuo. The residue was purified by chromatography (EtOAc/Hexane, 1 / 9 t o 3 / 7) , g i v i n g 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-

-101-

6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine as a colorless viscous oil (12.6 g, 50%). ¹H NMR d 1.24 (t, J=7.2 Hz, 3H), 2.81-2.98 (m, 3H), 3.97 (s, 3H), 5.14 (ABq, A=5.08, B= 5.20, J= 12.3 Hz, 2H), 6.28 (s, 3H), 7.03-7.29 (m, 8H), 7.35 (d, J=9.2 Hz, 2H), 8.26 (d, J=9.2 Hz, 2H).

5-(BENZYLOXYCARBONYL)-4-ETHYL-1,6-DIHYDRO-1-{N-[1-PHENYL]ETHYL}}-CARBOXAMIDO-2-METHOXY-6-(3,4-DIFLUOROPHENYL) PYRIMIDINE: To a stirred mixture of 5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (12.6 g, 22.9 mmol) in THF (150 mL) was added a solution of R-(+)- α -methyl benzylamine (3.53 mL, 27.1 mmol) at room temperature. The stirring was continued for 12 h and the solvent was removed in *vacuo*. The yellow residue was dissolved in chloroform (200 mL) and was washed with 10% K₂CO₃ solution (2x30 mL). The organic layer was dried over Na₂SO₄, filtered and solvent was removed in *vacuo*. The resulting mixture of diastereomers was separated by column chromatography (petroleum ether/ether, 9/1 to 4/1). The first major product to elute was (+)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[1-phenyl]-ethyl}}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. Colorless oil; R_f= 0.31 (petroleum ether/ether, 4/1); yield: 3.8 g (31%); [α]_D = +267.05 (c = 0.76, CHCl₃); ¹H NMR d 1.22 (t, J=7.5 Hz, 3H), 1.52 (d, J=6.9 Hz, 3H), 2.88 (q, J=6.0 Hz, 2H), 3.99 (s, 3H), 4.99 (m, 1H), 5.09 (ABq, A=5.00, B= 5.19, J= 12.6 Hz, 2H), 6.66 (s, 1H), 6.99-7.36 (m, 13H). The second major product to elute was (-)-5-(benzyloxycarbonyl)-4-ethyl-1,6-dihydro-1-{N-[2-phenyl]ethyl}}carboxamido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine. Colorless oil; R_f= 0.22 (petroleum

-102-

ether/ether, 4/1); yield: 3.20 g (26%); $[\alpha]_D = -146.89$ ($c = 0.38$, CHCl_3); $^1\text{H NMR}$ δ 1.22 (t, $J=7.2$ Hz, 3H), 1.49 (d, $J=6.6$ Hz, 3H), 2.88 (q, $J=6.0$ Hz, 2H), 3.94 (s, 3H), 5.03 (m, 1H), 5.11 (ABq, $A=5.02$, $B=5.19$, $J=12.6$ Hz, 2H),
5 6.68 (s, 1H), 6.91-7.34 (m, 13H).

(+)-5-(BENZYLOXYCARBONYL)-1,6-DIHYDRO-2-METHOXY-4-ETHYL-6-(3,4-DI-FLUOROPHENYL)PYRIMIDINE: To a stirred solution of (+)-5-(benz-yloxy carbonyl)-4-ethyl-1,6-dihydro-1-
10 {N-[2-phenyl)ethyl]}carbox-amido-2-methoxy-6-(3,4-difluorophenyl)pyrimidine (1.00 g, 1.83 mmol) in toluene (10 mL) was added 1,8-diazabicyclo[5,4,0]-undec-7-ene (0.120 mL, 0.810 mmol) at room temperature and the resulting solution was heated at reflux temperature for 5
15 h and then stirred for 12 h at room temperature. The solvent was evaporated and the residue was purified by flash column (EtOAc/Hexanes, 1/3), giving (+)-5-(benzyloxy carbonyl)-1,6- dihydro-2-methoxy-4-ethyl-6- (3,4-difluorophenyl)pyrimidine (0.560 g, 77%).

20 (+)-5-(BENZYLOXYCARBONYL)-4-ETHYL-1,6-DIHYDRO-2-METHOXY-6-(3,4-DI-FLUOROPHENYL)-1-[(4-NITROPHENYLOXY) CARBONYL]PYRIMIDINE: To a stirring solution of (+)-5-(benzyl oxy carbonyl)-1,6-dihydro-2-methoxy-4-ethyl-6-(3,4-difluorophen-yl)pyrimidine (17.0 g,
25 44.0 mmol) and 4-dimethylaminopyridine (6.99 g, 57.3 mmol) in CH_2Cl_2 (200 mL) was added 4-nitrophenyl chloroformate (11.6 g, 57.3 mmol) at room temperature. The reaction mixture was stirred for 12 h and then the solvent was removed in vacuo. The residue was purified by
30 chromatography (EtOAc/Hexane, 1/9 to 3/7), giving (+)-5-(benzyloxy carbonyl)-4-ethyl-1,6-dihydro-2-methoxy-6-(3,4- difluorophenyl)-1-[(4-nitrophenyloxy) carbonyl]pyrimidine as a viscous colorless oil (19.3 g,

-103-

76%).

5-METHYLBENZFUROXAN: 4-Methyl-2-nitroaniline (100 g, 0.650 mol) was suspended in saturated methanolic sodium hydroxide solution (1.50 L). This suspension was cooled (5 °C) and aqueous sodium hypochlorite until the red color disappeared. The resulting fluffy yellow precipitate was filtered, washed with cold water and recrystallized from ethanol, giving 5-methylbenzfuroxan (88.2 g, 89 % yield) as a pale yellow solid: ¹H NMR δ 2.39 (s, 3 H), 6.90-7.40 (br m, 3 H).

5-METHYLBENZOFURAZAN: To 5-Methylbenzfuroxan (88.2 g, 0.590 mol) in refluxing EtOH (75 mL) was added dropwise P(OEt)₃ (150 mL). Heating was continued at reflux temperature for 1 h. The solvent was removed in vacuo and the residue was shaken with water (200 mL) and allowed to stand overnight at (0-5 °C). The resulting brown solid was filtered, washed with water. The crude product was purified by flash chromatography, giving 5-methylbenzofurazan (70.0 g, 87 %) as white needles; ¹H NMR δ 2.41 (s, 1 H), 7.19 (dd, J=9.3, 1.1 Hz, 1 H), 7.48 (d, J=1.1 Hz, 1 H), 7.66 (d, J=9.3 Hz, 1 H).

5-DIBROMOMETHYLBENZOFURAZAN: An anhydrous solution of 5-methylbenzofurazan (70.0 g, 0.520 mol), N-bromosuccinamide (325 g), and benzoyl peroxide (0.50 g) in carbon tetrachloride (1.5 L) was heated at reflux temperature with stirring for 30 h. The reaction mixture was washed with water (2 X 500 mL), dried (NaSO₄), and the solvent was removed in vacuo. The residue was chromatographed (EtOAc/hexane, 1/150), giving 122 g (80%) of the title compound as a white solid: ¹H NMR δ 6.69 (s, 1 H), 7.69 (d, J=9.6 Hz, 1 H), 7.77 (s, 1 H), 7.89 (d, J=9.6 Hz, 1 H).

-104-

5-FORMYLBENZOFURAZAN: AgNO₃ (163 g) in 2 L of water was added to a refluxing mixture of dibromomethylbenzofurazan (122 g, 418 mmol) in EtOH (1 L). Heating at reflux temperature was continued for 2 h. The mixture was cooled, the precipitated AgBr was removed by filtration through Celite, and the solvent was concentrated. The resulting solution was extracted with toluene (10 X 100 mL), dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was chromatographed (EtOAc/hexane, 1/125), giving the title aldehyde (48.2 g, 78%) as a white solid: ¹H NMR δ 7.92 (m, 2H), 8.39 (s, 1 H), 10.10 (s, 1 H).

METHYL 2-((BENZOFURAN-5-YL)METHYLENE)-3-OXOBUTYRATE: A mixture of 5-formylbenzofurazan (0.60 g, 4.1 mmol), methyl acetoacetate (0.52 g, 4.5 mmol), piperidine (0.019 g, 0.23 mmol), and acetic acid (0.014 g, 0.23 mmol) in benzene (30 mL) was heated at reflux temperature (equipped with a Dean-Stark trap) for 8 h. Benzene was evaporated in vacuo, the residue was dissolved in ethyl acetate (80 mL) and washed with brine (50 mL), saturated potassium bisulfate solution (50 mL), and saturated sodium bicarbonate solution. The ethyl acetate solution was dried over magnesium sulfate, the solvent removed under reduced pressure and the residue was purified by column chromatography (EtOAc/hexane, 1/9 to 3/20). The desired product was obtained as oil (0.98 g, 98%) and was used in the next step without any further characterization.

30

6-(BENZOFURAZAN-5-YL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-4-METHYLPYRIMIDINE: A mixture of methyl 2-((benzofuran-5-yl)-methylene)-3-oxobutyrates (1.02 g, 4.10 mmol), O-methylisourea hydrogen sulfate (1.06 g, 6.20

-105-

mmol), and NaHCO_3 (1.30 g, 16.4 mmol) in DMF (15 mL) was stirred and heated at 70 °C for 16 h. The mixture was cooled, diluted with EtOAc (50 mL) and washed with water (5X 50 mL), brine (50 mL) and dried over magnesium sulfate.

5 The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc/hexane, 1/9 to 1/5), giving the desired product as an oil (0.520 g, 43%):

^1H NMR δ 2.38 and 2.42 (2 s, 3 H), 3.60 and 3.66 (2 s, 3 H), 3.74 and 3.82 (2 s, 3 H), 5.53 and 5.68 (2 s, 1 H), 6.31

10 and 6.32 (br s, 1 H), 7.0-7.8 (m, 3 H).

6-(BENZOFURAZAN-5-YL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-4-METHYL-1-[(4-NITROPHENYLOXY)CARBONYL]PYRIMIDINE:

15 To a solution of 6-(benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (0.485 g, 1.6 mmol) and 4-dimethylaminopyridine (0.200 g, 1.64 mmol) in CH_2Cl_2 (20 mL) at 0-5 °C was added 4-nitrophenyl chloroformate (0.307 g, 1.52 mmol). The mixture was then

20 allowed to warm to room temperature. After 12 h, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc/hexane, 1/9 to 3/20), giving the desired product as white crystals (0.665 g, 89%); mp 180-183 °C; ^1H NMR δ 2.54 (s, 3 H), 3.75 (s, 3 H), 3.98 (s,

25 3 H), 6.37 (s, 1 H), 7.40 (d, $J=9.3$ Hz, 2 H), 7.52 (d, $J=9.0$ Hz, 1 H), 7.68 (s, 1 H), 7.84 (d, $J=9.0$ Hz, 1 H), 8.32 (d, $J=9.3$ Hz, 2 H).

30 (+) and (-)-6-(BENZOFURAZAN-5-YL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-1-[N-(S)-1-(1-PHENYLETHYL)]-4-METHYLPYRIMIDINE: A solution of 6-(benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (800 mg, 1.71 mmol)

-106-

and (S)-(-)- α -methylbenzylamine (269 mg, 2.22 mmol) in THF (50 mL) was stirred at room temperature for 12 h. The THF was removed in vacuo and the residue was dissolved in EtOAc (100 mL), washed by 10% aqueous K_2CO_3 solution (3x50 mL), brine (50 mL) and dried (Na_2SO_4). After removal of the solvent, the residue was purified by chromatography (EtOAc/hexane, 1/20 to 3/20), separating the two diastereomers. The isomers of 6-(benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-1-[N-(S)-1-(1-phenylethyl)]-4-methylpyrimidine were obtained as colorless oils. 1st Isomer (367 mg, 47.7%): $[\alpha]_D = +278$ ($c=0.50$, $CHCl_3$); 1H NMR δ 1.54 (d, $J=6.9$ Hz, 3H), 2.45 (s, 3H), 3.68 (s, 3H), 3.99 (s, 3H), 5.02 (quintet, $J=6.9$ Hz, 1H), 6.71 (s, 1H), 6.89 (d, $J=6.6$ Hz, 1H), 7.2-7.9 (m, 8H). 2nd Isomer (205 mg, 26.6%): $[\alpha]_D = -81$ ($c=0.43$, $CHCl_3$); 1H NMR δ 1.52 (d, $J=6.6$ Hz, 3H), 2.48 (s, 3H), 3.71 (s, 3H), 3.96 (s, 3H), 5.00 (quintet, $J=6.6$ Hz, 1H), 6.74 (s, 1H), 6.90 (d, $J=6.5$ Hz, 1H), 7.2-7.9 (m, 8H).

6-(BENZOFURAZAN-5-YL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-4-METHYLPYRIMIDINE: A solution of the 1st isomer of 6-(benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbon-yl-1-[N-(S)-1-(1-phenylethyl)]-4-methylpyrimidine (960 mg, 2.14 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (107 mg, 0.705 mmol) in toluene (50 mL) was stirred at 100 °C for 5 h. After cooling to room temperature, toluene was removed in vacuo and the residue was purified by chromatography (EtOAc/hexane, 1/9 to 3/7). 6-(Benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine was obtained as a colorless oil (635 mg, 98.3%). 1H NMR δ 2.38 (s, 3H), 3.66 (s, 3H), 3.74 (s, 3H), 5.68 (s, 1H), 6.32 (br s, 1H), 7.0-7.8 (m, 3H).

-107-

6-(BENZOFURAZAN-5-YL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-4-METHYL-1-(4-NITROPHENOXY)CARBONYLPYRIMIDINE: To a solution of 6-(benzofuran-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (0.485 g, 1.60 mmol) and 4-dimethylamino-pyridine (0.200 g, 1.60 mmol) in CH_2Cl_2 (20 mL), at 0-5 °C, was added 4-nitrophenyl chloroformate (0.307 g, 1.52 mmol). After addition, the mixture was allowed to warm to room temperature. After 12 hours, the solvent was evaporated and the residue was purified by flash column chromatography (EtOAc/hexane, 1/9 to 3/20), giving the desired product as white crystals (0.665 g, 89%): mp 180-183 °C; ^1H NMR δ 2.54 (s, 3 H), 3.75 (s, 3 H), 3.98 (s, 3 H), 6.37 (s, 1 H), 7.40 (d, J = 9.3 Hz, 2 H), 7.52 (d, J = 9.0 Hz, 1 H), 7.68 (s, 1 H), 7.84 (d, J = 9.0 Hz, 1 H), 8.32 (d, J = 9.3 Hz, 2 H); $[\alpha]_D = +266$ ($c=2.70$, CH_2Cl_2).

METHYL 2-((3,4-DIFLUOROPHENYL)METHYLENE)-3-OXOBUTYRATE: A mixture of 3,4-difluorobenzaldehyde (14.2 g, 0.100 mol), methyl acetoacetate (12.2 g, 0.105 mol), piperidine (0.430 g, 5 mmol), and acetic acid (0.30 g, 5 mmol) in benzene (150 mL) was stirred and heated at reflux temperature (equipped with a Dean-Stark trap) for 8 h. The benzene was evaporated and the residue was dissolved in ethyl acetate (200 mL). The resulting solution was washed with brine (50 mL), saturated potassium bisulfate solution (50 mL), and saturated sodium bicarbonate solution. The ethyl acetate solution was dried over magnesium sulfate and the solvent was removed under reduced pressure. The residue was purified by column chromatography (EtOAc/hexane, 1/9 to 3/20), giving the desired product as a yellow oil (9.80 g, 41%) which was used in the subsequent step without any further characterization.

-108-

6-(3,4-DIFLUOROPHENYL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-4-METHYLPYRIMIDINE: A mixture of methyl 2-((3,4-difluorophenyl)-methylene)-3-oxobutyrates (8.80 g, 36.3 mmol), O-methylisourea hydrogen sulfate (9.40 g, 546 mmol), and NaHCO₃ (12.3 g, 146 mmol) in DMF (30 mL) was heated at 70 °C with stirring for 16 h. The mixture was cooled, diluted with EtOAc (300 mL) and washed with water (5 X 300 mL), brine (300 mL), and dried over magnesium sulfate. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc/hexane, 1/9 to 3/7) as the gradient eluent, giving the desired product as an oil (3.82 g, 35%).

6-(3,4-DIFLUOROPHENYL)-1,6-DIHYDRO-2-METHOXY-5-METHOXYCARBONYL-4-METHYL-1-[(4-NITROPHENOXY)CARBONYL]PYRIMIDINE: 4-Nitrophenyl chloroformate (1.82 g, 9.04 mmol) was added to a solution of 6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methylpyrimidine (2.82 g, 9.46 mmol) and 4-dimethylaminopyridine (1.16 g, 9.52 mmol) in CH₂Cl₂ (50 mL), at 0-5 °C and the mixture was then allowed to warm to room temperature. After 12 h, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc/hexane, 1/9 to 3/20), giving the desired product as white crystals (3.72, 85%): mp 172-174 °C.

6-(3,4-DIFLUOROPHENYL)-1,2,3,6-TETRAHYDRO-2-OXO-5-METHOXYCARBONYL-4-METHYL-1-(4-NITROPHENOXY)CARBONYLPYRIMIDINE: Aqueous 6 N hydrochloric acid (10 mL) was added to a stirring solution of 6-(3,4-difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (10.0 g) in THF (200 mL) at room temperature. The stirring was continued for 3 h. The solvent was evaporated and the residue was dried under vacuum, giving the desired product as a white powder (9.70

-109-

g, 100%): mp 185-186 °C.

(+)-1-(3-BROMO-PROPYLCARBAMOYL)-6-(3,4-DIFLUOROPHENYL)-4-METHYL- 2-OXO-1,6-DIHYDRO-PYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER: A solution of 10% aqueous HCl (5 mL) was added to a stirring solution of (+)-6-(3,4-difluorophenyl)-1,6-dihydro- 2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenoxy)-carbonyl]pyrimidine (4.10 g, 9.10 mmol) in THF (20 mL) at room temperature and the resulting solution was stirred overnight. The THF was removed *in vacuo* and the resulting residue was extracted with EtOAc (3 X 20 mL), washed with brine (10 mL) and then dried over Na₂SO₄. The solvent was removed *in vacuo*, giving (+)-6-(3,4-di-fluorophenyl)-1,6-dihydro-2- oxo-5-methoxycarbonyl-4-methyl-1- [(4-nitrophenoxy)carbonyl]pyrimidine as a viscous oil (3.8 g, 8.5 mmol). The oil was dissolved in THF (20 mL) and 3-bromo-propylamine hydrobromide (2.33 g, 10.8 mmol) and NaHCO₃ (1.81 g, 21.5 mmol) were added. The resulting suspension was stirred at room temperature overnight. The THF was removed *in vacuo* and the resulting residue was dissolved in water (10 mL) and then extracted with EtOAc (3 X 20 mL). The EtOAc extracts were combined, dried over Na₂SO₄, filtered and the solvent was removed , giving (+)-1-(3-bromo-propylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydropyrimidine-5-carboxylic acid methyl ester (3.28 g, 83%): ¹H NMR δ 2.05-2.15 (m, 2 H), 2.43 (s, 3 H), 3.40-3.56 (m, 4 H), 3.72 (s, 3 H), 6.69 (s, 1 H), 7.08-7.27 (m, 3 H), 7.57 (br s, 1 H), 8.84 (br t, 1 H). Anal. Calcd for C₁₇H₁₈N₃O₄ F₂Br: C, 45.76; H, 4.07; N, 9.42. Found: C, 45.70; H, 3.99; N, 9.16.

3-((3,4,5-TRIFLUOROPHENYL)METHYLENE)-2,4-PENTANEDIONE: A stirring mixture of 3,4,5-trifluorobenzaldehyde (4.20 g,

-110-

26.2 mmol), 2,4-pentanedione (2.62 g, 26.2 mmol), piperidine (0.430 g, 5.00 mmol) in benzene (150 mL) was heated at reflux temperature (equipped with a Dean-Stark trap) for 8 h. The benzene was evaporated and the yellow oily residue, 2-((3,4,5-trifluorophenyl)methylene)-2,4-pentanedione, was used in the next step without further purification.

6-(3,4,5-TRIFLUOROPHENYL)-1,6-DIHYDRO-2-METHOXY-5-ACETYL-4-METHYLPYRIMIDINE: A mixture of 2-((3,4,5-trifluorophenyl)methylene)-2,4-pentanedione (26.2 mmol), O-methylisourea hydrogen sulfate (3.22 g, 39.3 mmol), and NaHCO₃ (6.6 g, 78.6 mmol) in EtOH (400 mL) was stirred and heated at 95-100 °C for 6 h. The mixture was filtered and the solid residue was washed with ethanol (100 mL). The solvent was evaporated from the combined filtrates and the crude product was purified by flash column chromatography (EtOAc/hexane, 1/9 to 1/4), giving the desired product as an oil (2.80 g, 36%).

6-(3,4,5-TRIFLUOROPHENYL)-1,6-DIHYDRO-2-METHOXY-5-ACETYL-4-METHYL-1-[(4-NITROPHENYLOXY)CARBONYL]PYRIMIDINE: 4-Nitrophenyl chloroformate (1.89 g, 9.38 mmol) was added to a solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methylpyrimidine (2.80 g, 9.38 mmol) and pyridine (10 mL) in CH₂Cl₂ (200 mL) at 0-5 °C, and the resulting mixture was allowed to warm to room temperature. After 12 h, the solvent was evaporated and the residue was purified by flash chromatography (dichloro-methane/EtOAc, 1/9 to 3/20), giving the desired product as a white powder (4.00 g, 92%).

6-(3,4,5-TRIFLUOROPHENYL)-1,2,3,6-TETRAHYDRO-2-OXO-5-ACETYL-4-METHYL-1-[(4-NITROPHENYLOXY)CARBONYL]PYRIMIDINE: A solution of 6 N aqueous HCl (4 mL) was added to a stirring

-111-

5 solution of 6- (3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methyl- 1-[(4-nitrophenyloxy)carbonyl]pyrimidine (4.00 g, 8.63 mmol) in THF (100 mL) at 0-5 °C, and the mixture was allowed to warm to room temperature. After 2 h, solvent was evaporated and the product dried under vacuum. The product was obtained as a pure single component and used in the next step without any further purification (3.88 g, 100%).

10 Procedures for the Synthesis of the Piperidine Intermediates

(reference for the general procedure for Pd coupling of vinyl triflate and boronic acids or tributyl tin reagents: See, Wuston, Wise Synthesis (1991), 993)

15

TERT-BUTYL 4-[[(TRIFLUOROMETHYL) SULFONYL] OXY]-

1,2,3,6-TETRA-HYDRO-1-PYRIDINECARBOXYLATE: *n*-Butyllithium (17.6 mL, 44.2 mmol, 2.5 M in hexanes) was added to a solution of diisopropyl amine (96.2 mL, 44.2 mmol) in 40 mL of dry THF at 0 °C and stirred for 20 minutes. The reaction mixture was cooled to -78 °C and tert- butyl 4-oxo-1-piperidinecarboxylate (40.0 mmol) in THF (40 mL) was added dropwise to the reaction mixture and stirred for 30 minutes. Ti_2NPh (15.0 g, 42.0 mmol) in THF (40 mL) was added dropwise to the reaction mixture and the mixture was stirred at 0 °C overnight. The reaction mixture was concentrated in vacuo, re-dissolved in hexanes/EtOAc (9/1), passed through a plug of alumina and washed with hexanes/EtOAc (9/1). The combined extracts were concentrated to yield 16.5 g of the desired product that was contaminated with a small amount of Ti_2NPh . ^1H NMR δ 5.77 (s, 1 H), 4.05 (dm, 2 H, $J=3.0$ Hz), 3.63 (t, 2 H, $J=5.7$ Hz), 2.45 (m, 2 H), 1.47 (s, 9 H).

-112-

TERT-BUTYL 4-[3-(ACETYLAMINO)PHENYL]-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE: A mixture of saturated of aqueous Na_2CO_3 solution (25 mL), tert-butyl 4-[[trifluoromethyl)sulfonyl]oxy]-1,2,3,6-tetrahydro-1-pyridine-carboxylate (20 mmol), 3-acetamidophenylboronic acid (30 mmol) and tetrakis-triphenylphosphine palladium (0) (1.15 g) and dimethoxyethane (40 mL) was heated at reflux temperature overnight. The organic layer of the cooled reaction mixture was separated and the aqueous layer was washed with ethyl acetate (3X). The combined organic extracts were dried and concentrated *in vacuo*. The crude product was chromatographed, giving the desired product $^1\text{H NMR } \delta$ 8.11 (br s, 1 H), 7.57 (br s, 1 H), 7.41 (br δ , 1 H, $J=7.8$ Hz), 7.25 (apparent t, 1 H, $J=7.8$ Hz), 7.08 (br d, 1 H, $J=7.8$ Hz), 5.99 (b s, 1 H), 4.03 (br m, 2 H, $J=2.7$ Hz), 3.59 (t, 2 H, $J=5.7$ Hz), 2.46 (m, 2 H), 2.16 (s, 3 H), 1.49 (s, 9 H).

N1-[3-(1,2,3,6-TETRAHYDRO-4-PYRIDINYL)PHENYL]ACETAMIDE: A solution of 4 M HCl in dioxane (10 mL) was added to tert-butyl 4-[3-(acetylamino)phenyl]-1,2,3,6-tetrahydro-1-pyridinecarboxyl-ate (8.25 mmol) in dichloromethane (30 mL). The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, giving the desired product as the hydrochloride salt (2.1 g). $^1\text{H NMR } \delta$ 7.41-7.00 (m, 4 H), 6.10 (br, 1 H), 3.55 (m, 2 H), 3.16 (t, 2 H, $J = 5.7$ Hz), 2.44 (m, 2 H), 2.19 (s, 3 H).

30

TERT-BUTYL N-(3-BROMOPROPYL)CARBAMATE: Prepared from 3-bromopropylamine hydrobromide and BOC_2O in the presence of base in dichloromethane: $^1\text{H NMR } \delta$ 5.07 (br, 1 H), 3.31 (t, 2 H, $J=6.6$ Hz), 3.12 (apparent br q, 2 H, $J=6.0$ Hz), 1.92

-113-

(p, 2 H, J=6.6 Hz), 1.30 (s, 9H).

REACTION OF N1-[3-(1,2,3,6-TETRAHYDRO-4-PYRIDINYL) PHENYL]
ACETAMIDE WITH TERT-BUTYL N-(3-BROMOPROPYL) CARBAMATE

5

TERT-BUTYL N-(3-{4-[3-(ACETYLAMINO) PHENYL]-

1,2,3,6-TETRAHYDRO- 1-PYRIDINYL} PROPYL) CARBAMATE: A

solution of N1-[3-(1,2,3,6- tetrahydro-4-pyridinyl)

phenyl]acetamide hydrochloride (8.24 mmol), tert-butyl

10 N-(3-bromopropyl)carbamate and potassium carbonate (33

mmol) in dry dioxane (30 mL) was heated at reflux

temperature overnight. The solids were removed by

filtration, the solution was concentrated in vacuo and the

product was chromatographed, giving the desired product

15 (110 mg). ¹H NMR δ 7.65 (s, 1 H), 6.98 (s, 1 H), 7.45 (d, 1

H, J=7.8 Hz), 7.16 (apparent t, 1 H, J=7.8 Hz), 7.10 (d, 1

H, J=7.8 Hz), 6.02 (s, 1 H), 5.23 (b, 1 H), 3.40 (b, 2 H),

3.30-1.80 (m, 10 H), 2.18 (s, 3 H), 1.45 (s, 9 H).

20 Deprotection of BOC:

N1-[3-[1-(3-AMINOPROPYL)-1,2,3,6-TETRAHYDRO-4-PYRIDINYL]P

HENYL]ACETAMIDE: A 1:1 solution of TFA:CH₂Cl₂ (5 mL) was

added to tert-butyl N-(3-{4-[3-(acetyl amino)phenyl]-

1,2,3,6-tetrahydro-1- pyridinyl}propyl)carbamate in

25 dichloromethane (5 mL). The resulting solution was stirred

at room temperature for 1-3 days, saturated NaHCO₃ was

added until pH > 6, the organic layer was separated, and

dried in vacuo, giving the desired product (45 mg): ¹H NMR

δ 7.68 (br, 1 H), 7.35 (dm, 1 H, J=7.8 Hz), 7.25 (apparent

30 t, 1 H, J=7.8 Hz), 7.15 (dm, 1 H, J=7.8 Hz), 6.12 (m, 1 H),

3.22 (m, 2 H), 3.03 (t, 2 H, J=7.3 Hz), 2.78 (t, 2 H, J=5.5

Hz), 2.70-2.50 (m, 4 H), 2.10 (s, 3 H), 1.87 (p, 2 H, J=7.3

Hz).

-114-

TERT-BUTYL 4-[3-(ACETYLAMINO)PHENYL]-1-

PIPERIDINECARBOXYLATE: A mixture tert-butyl

4-[3-(acetylamino)phenyl]-1,2,3,6-tetra-hydro-1-

pyridinecarboxylate (710 mg) and 5% Pd/C (100 mg) in EtOH

5 (10 mL) was hydrogenated (balloon technique) at room

temperature overnight. The reaction mixture was passed

through a pad of Celite 545 and the pad of Celite was

washed with ethanol. The combined ethanol extracts were

concentrated and chromatographed, giving the desired

10 product (660 mg). ¹H NMR δ 7.80 (s, 1 H), 7.41-7.20 (m, 3

H), 6.94 (d, 1 H, J=7.5 Hz), 4.21 (m, 2 H), 2.75 (m, 2 H),

2.62 (m, 1 H), 2.16 (s, 3 H), 1.78 (m, 2 H), 1.56 (m, 2 H),

1.48 (s, 9 H).

15 N1-[3-(4-PIPERIDYL)PHENYL]ACETAMIDE: A solution of HCl in

dioxane (4N, 5 mL) was added to tert-butyl 4-[3-

(acetylamino)-phenyl]-1-piperidinecarboxylate (660 mg) in

dry dichloromethane (15 mL). The reaction mixture was

stirred at room temperature overnight and concentrated in

20 *vacuo*, giving the desired product (550 mg): mp 102-104 °C;¹H NMR δ 2.02 (d, J=13.2 Hz, 2H), 2.11-2.45 (m, 5H),

2.67-2.77 (m, 1H), 3.00-3.10 (m, 2H), 3.51 (d, J=10.5 Hz,

2H), 6.94 (d, J=7.5 Hz, 1H), 7.20-7.46 (m, 3H), 7.60 (s,

1H).

25

TERT-BUTYL N-(3-{4-[3-(ACETYLAMINO)PHENYL]

PIPERIDINO}PROPYL)-CARBAMATE:

A solution of

N1-[3-(4-piperidyl)phenyl]acetamide (550 mg, 0.210 mmol),

tert-butyl N-(3-bromopropyl)-carbamate (550 mg, 0.230

30 mmol), K₂CO₃ (1.10 g, 0.890 mmol), diisopropylethyl amine

(1.50 mL) and a few crystals of KI in dioxane (20 mL) was

heated at reflux temperature for 2 days. The precipitated

salts were removed by filtration, concentrated in *vacuo* and

the crude product was chromatographed, giving the desired

-115-

product (340 mg). ^1H NMR δ 8.15 (s, 1 H), 7.47-7.44 (m, 2 H), 7.22 (t, 1 H, $J=7.8$ Hz), 6.94 (d, 1 H, $J=7.8$ Hz), 5.53 (b, 1 H), 3.23 (b, 6 H), 2.80-1.60 (m, 9 H), 2.20 (s, 3 H), 1.45 (s, 9 H).

5

N1-{3-[1-(3-AMINOPROPYL)-4-PIPERIDYL]PHENYL}ACETAMIDE: TFA (1.0 mL) was added to a solution of tert-butyl N-(3-{4-[3-(acetyl-amino)phenyl]piperidino} propyl)carbamate (340 mg) in dry dichloromethane (10 mL) and stirred at room temperature for 5 h. A 10% aqueous solution of KOH was added to the reaction mixture until pH > 6 and then the dichloromethane was removed in vacuo. The aqueous layer was frozen and lyophilized, giving a solid which was then extracted with methanol. Removal of methanol gave the desired product (120 mg) as an oil. ^1H NMR δ 8.56 - 8.46 (s, 1H), 7.43 - 7.30 (m, 2H), 7.23 - 7.16 (apparent t, 1H, $J=7.5$ Hz), 6.95 - 6.92 (m, 1H), 3.03 - 2.99 (m, 2H), 2.77 - 2.73 (t, 2H, $J = 6.6$ Hz), 2.50-1.60 (m, 10 H), 2.13 (s, 3 H).

20

1-BENZYL-4-HYDROXY-4-(4-FLUORO-2-METHYLPHENYL)PIPERIDINE: ^1H NMR δ 7.40-7.26 (M, 5 H), 6.91-6.76 (m, 3 H), 3.57 (s, 2 H), 2.83- 2.72 (m, 2 H), 2.61 (s, 3 H), 2.58-2.43 (m, 2 H), 2.23-2.12 (m, 2 H).

25

1-BENZYL-4-(4-FLUORO-2-METHYLPHENYL)-1,2,3,6-TETRAHYDROPIRIDINE: ^1H NMR δ 7.41-7.26 (m, 5 H), 7.05 (dd, 1 H, $J=6.0$, 8.1 Hz), 6.87-6.80 (m, 2 H), 5.52-5.50 (m, 2 H), 3.65 (s, 2 H), 3.13 (q, 2 H, $J=3.3$ Hz), 2.69-2.66 (t, 2 H, $J=5.1$ Hz), 2.35-2.31 (m, 2 H), 2.27 (s, 3 H).

30

4-(4-FLUORO-2-METHYLPHENYL)PIPERIDINE: ^1H NMR δ 7.17 (t, 1

-116-

H, $J=7.2$ Hz), 6.83-6.80 (m, 2 H), 3.22 (m, 2 H), 2.81-2.73 (m, 2 H), 2.66 (br s, 1 H), 2.33 (s, 3 H), 1.80-1.60 (m, 4 H).

5 1-BENZYL-4-(3,4,5-TRIFLUOROPHENYL)-1,2,3,6-TETRAHYDROPYRIDINE: ^1H NMR δ 7.50-7.20 (m, 7 H), 5.67 (m, 1 H), 3.69 (s, 2 H), 3.19 (apparent q, 2 H, $J=2.7$ Hz), 2.75 (t, 2 H, $J=5.7$ Hz), 2.34 (m, 2 H).

10 4-(3,4,5-TRIFLUOROPHENYL)PIPERIDINE: mp 197-199 °C; ^1H NMR δ 2.05 (d, $J=13.2$ Hz, 2H),), 2.33 (dd, $J=25.5$ Hz, $J=12.9$ Hz, 2H), 3.06-3.23 (m, 3H), 3.73 (d, $J=12.0$ Hz, 2H), 6.94-7.04 (m, 2H).

15 4-(3,4,5-TRIFLUOROPHENYL)PIPERIDINE: ^1H NMR δ 7.20-6.80 (m, 2 H), 3.73 (m, 2 H), 3.14 (m, 3 H), 2.33 (m, 2 H), 2.05 (m, 2 H).

TERT-BUTYL N-3-[4-(3,4,5-TRIFLUOROPHENYL)PIPERIDINO]

20 PROPYL-CARBAMATE: ^1H NMR δ 6.91 (m, 2 H), 5.62 (b, 1 H), 4.31 (t, 2 H, $J=5.4$ Hz), 3.63 (m, 2 H), 3.39 (dt, 2 H, $J=2.1, 6.0$ Hz), 3.40-2.70 (m, 7 H), 2.46 (t, 2 H, $J=6.9$ Hz), 2.10-1.60 (m, 4 H), 1.45 (s, 9 H).

25 3-[4-(3,4,5-TRIFLUOROPHENYL)PIPERIDINO]-1-PROPANAMINE: ^1H NMR δ 6.93 (m, 2 H), 4.30 (b, 1 H), 3.36 (b, 1 H), 3.06 (m, 2 H), 2.77 (m, 2 H), 2.43 (m, 2 H), 2.20-1.40 (m, 9 H).

30 1-BENZYL-4-(5-FLUORO-2-METHOXYPHENYL)-4-PIPERIDINOL: ^1H NMR δ 7.40-6.80 (m, 8 H), 3.94 and 3.85 (s, 3 H), 3.61 and 3.58 (s, 2 H), 2.80-1.90 (m, 8 H).

1-BENZYL-4-(5-FLUORO-2-METHOXYPHENYL)-1,2,3,6-TETRAHYDRO

-117-

YRIDINE: ^1H NMR δ 7.40-6.70 (m, 8 H), 5.84 (m, 1 H), 3.77 (s, 3 H), 3.64 (s, 2 H), 3.17 (m, 2 H), 2.68 (t, 2 H, $J=5.7$ Hz), 2.54 (m, 2 H).

5 4-(5-FLUORO-2-METHOXY)PHENYL PIPERIDINE: mp 254-258 $^{\circ}\text{C}$; ^1H NMR δ 1.53-1.68 (m, 2H), 1.79 (d, $J=11.7$ Hz, 2H), 2.12 (dt, $J=2.1$ Hz, $J=11.7$ Hz, 1H), 2.77 (dt, $J=1.8$ Hz, $J=12.3$ Hz, 1H), 2.90-3.05 (m, 1H), 3.10-3.22 (m, 2H), 3.68 (s, 1H), 3.79 (s, 3H), 6.72-6.93 (m, 3H). Anal. Calcd. For
10 $\text{C}_{12}\text{H}_{17}\text{NOFCl} + 0.14 \text{CH}_2\text{Cl}_2$: C, 56.60; H, 6.76; N, 5.44. Found: C, 56.60; H, 6.92; N, 5.28.

TERT-BUTYL N-3-[4-(5-FLUORO-2-METHOXYPHENYL)PIPERIDINO]
15 PROPYL-CARBAMATE: ^1H NMR δ 6.90-6.70 (m, 3 H), 5.76 (b, 1 H), 3.80 (s, 3 H), 3.68 (m, 1 H), 3.40-2.90 (m, 4 H), 2.45 (t, 2 H, $J=6.6$ Hz), 2.20-1.60 (m, 9 H), 1.45 (s, 9 H).

3-[4-(5-FLUORO-2-METHOXYPHENYL)PIPERIDINO]-1-PROPANAMINE:
20 ^1H NMR δ 7.00-6.80 (m, 3 H), 3.80 (s, 3 H), 3.05 (d, 2 H, $J=11.4$ Hz), 2.76 (t, 2 H, $J=6.9$ Hz), 2.43 (dd, 2 H, $J=7.8$ Hz), 2.05 (dt, 2 H, $J=2.4$, 11.7 Hz), 1.90-1.20 (m, 10 H).

TERT-BUTYL 4-(1-NAPHTHYL)-1,2,3,6-TETRAHYDRO-1-
25 PYRIDINECARBOXYL-ATE: ^1H NMR δ 8.00-7.80 (m, 2 H), 7.76 (d, 1 H, $J=8.1$ Hz), 7.50-7.44 (m, 2 H), 7.42 (d, 1 H, $J=8.1$ Hz), 7.27 (d, 1 H, $J=8.1$ Hz), 5.76 (br, 1 H), 4.14 (m, 2 H), 4 or 3.29 (t, 2 H, $J=5.7$ Hz), 2.52 (br m, 2 H), 1.53 (s, 9H).

30 4-(1-NAPHTHYL)PIPERIDINE: HCl salt; mp 330-332 $^{\circ}\text{C}$; ^1H NMR δ 1.66-1.70 (m, 2H), 2.20-2.26 (m, 2H), 2.30-2.43 (m, 2H), 2.72-2.84 (m, 1H), 3.15-3.26 (m, 2H), 7.42-7.56 (m, 4H), 7.78 (d, $J=8.1$ Hz, 1H), 7.90 (d, $J=8.1$ Hz, 1H), 8.04 (d,

-118-

J=8.1 Hz, 1H). Anal. Calcd. For $C_{15}H_{18}NOCl + 0.20 CH_2Cl_2$: C, 68.96; H, 7.00; N, 5.29. Found: C, 68.64; H, 7.04; N, 5.24.

5 TERT-BUTYL N-3-[4-(1-NAPHTHYL)PIPERIDINO]PROPYLCARBAMATE:
 1H NMR δ 8.09 (d, 1 H, J=8.4 Hz), 7.86 (dd, 1 H, J=1.8, 7.5 Hz), 7.71 (dd, 1 H, J=2.4, 6.9 Hz), 7.60-7.30 (m, 4 H), 6.31 (br, 1 H), 5.75 (br, 1 H), 4.26 (t, 1 H, J=5.4 Hz), 3.40-3.00 (m, 6 H), 2.54 (t, 2 H, J=6.9 Hz), 2.24 (dt, 2 H, J= 3.0, 11.4 Hz), 2.00-1.60 (m, 6 H), 1.45 (s, 9 H).

15 4-(3-METHYL-2-PYRIDYL)-4-PIPERIDINOL: 1H NMR δ 8.21 (dd, 1 H, J=1.2, 4.5 Hz), 7.36 (dd, 1 H, J=6.6, 7.8 Hz), 7.02 (dd, 1 H, J=4.8, 7.5 Hz), 3.07 (dt, 2 H, J=2.7, 12.3 Hz), 2.89 (m, 2 H), 2.46 (s, 3 H), 2.22 (dt, 2 H, J=4.8, 12.3 Hz), 1.39 (dm, 2 H, J=12.3 Hz).

20 TERT-BUTYL 4-(3-METHYL-2-PYRIDYL)-1,2,3,6-TETRAHYDRO-1-PYRIDINE-CARBOXYLATE: 1H NMR δ 8.16 (dd, 1 H, J=1.2, 3.3 Hz), 7.51 (dm, 1 H, J=7.5 Hz), 7.15 (dd, 1 H, J=4.8, 7.5 Hz), 5.73 (br, 1 H), 4.01 (m, 2 H), 3.59 (t, 2 H, J=5.7 Hz), 2.40 (m, 2 H), 1.44 (s, 9 H).

25 T E R T - B U T Y L
N-3-[4-(3-METHYL-2-PYRIDYL)PIPERIDINO]PROPYLCARBAMATE: 1H NMR δ 8.37 (dd, 1 H, J=4.2, 4.8 Hz), 7.51 (dd, 1 H, J=7.2, 7.5 Hz), 7.20 (dd, 1 H, J=4.5, 7.5 Hz), 6.73 (br, 1 H), 3.26 (m, 4 H), 3.05 (d, 2 H, J=12.0 Hz), 2.80-2.40 (m, 4 H), 2.61 (s, 3 H), 1.82 (p, 2 H, J=6.3 Hz), 1.54 (d, 2 H, J= 12.0 Hz).

T E R T - B U T Y L
4-(3-METHOXYPHENYL)-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE: 1H NMR δ 7.23 (t, 1 H, J= 8.1 Hz), 6.96 (d, 1 H,

-119-

J=7.5 Hz), 6.89 (d, 1 H, J=1.8 Hz), 6.80 (dd, 1 H, J=2.4, 8.1 Hz), 6.02 (br, 1 H), 4.20-4.00 (m, 3 H), 3.80 (s, 3 H), 3.62 (t, 2 H, J=5.7 Hz), 2.51 (br, 2 H), 1.49 (s, 9 H).

- 5 1-BENZYL-4-METHYL-PIPERIDIN-4-OL: Methyllithium (1.4 M in Et₂O, 54.0 mL) was added to a solution of 1-benzyl-4-piperidone (5.00 mL, 27.0 mmol) in anhydrous ether at -78 °C under argon. Stirring was continued at -78 °C for 1.5 hours. Ether (200 mL) and water (40 mL) were added,
-

-120-

(m, 2 H), 2.55 (m, 2 H), 3.50 (s, 2 H), 7.25 (m, 1 H), 7.35 (m, 4 H); ^{13}C NMR δ 36.82, 37.65, 50.95, 54.93, 64.08, 126.19, 126.51, 127.59, 128.83, 128.95, 129.05, 129.89, 139.24.

5

4-METHYL-4-PHENYLPIPERIDINE: Freshly prepared methanolic formic acid solution (4.4% by weight, 70 mL) was added to 1-benzyl-4-methyl-4-phenylpiperidine (3.23 g, 12.2 mmol). To the resulting solution was added 10% palladium on carbon (2.00 g). The mixture was stirred at room temperature for 24 hours. The solid was filtered out and washed with MeOH (30 mL), H_2O (15 mL), CH_2Cl_2 (30 mL) and MeOH (15 mL). The combined filtrate and washings were concentrated, and the residue was dissolved in CH_2Cl_2 (50 mL) and H_2O (10 mL). The aqueous phase was adjusted to pH 11 by addition of 1 N aqueous NaOH. The organic phase was separated, dried over magnesium sulfate and concentrated. The residual oil was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH}/2\text{ N NH}_3$ in MeOH 100/4/0 to 100/20/10), giving 1-benzyl-4-methyl-4-phenylpiperidine (1.20 g) and 1.10 g (51%, 82% based on consumed starting material) of 4-methyl-4-phenylpiperidine: ^1H NMR δ 1.24 (s, 3 H), 1.71 (m, 2 H), 2.06 (m, 2 H), 2.82 (m, 3 H), 2.94 (m, 2 H), 7.19 (m, 1 H), 7.32 (m, 4 H); ^{13}C NMR δ 37.22, 38.54, 43.44, 47.74, 126.31, 127.43, 129.01, 149.73.

25

3-AMINOPROPYL-4-METHYL-4-PHENYLPIPERIDINE: A solution of 4-methyl-4-phenylpiperidine (1.00 g, 5.70 mmol), 3-bromopropylamine hydrobromide (1.87 g, 8.55 mmol) and potassium carbonate (1.97 g, 14.2 mmol) in refluxing dioxane (20 mL) was stirred for 36 hours. After removal of the solvent, water (50 mL) was added and the pH adjusted to 11-12 by the addition of 1 N aqueous NaOH. The mixture was extracted

30

-121-

with CH_2Cl_2 (150 mL + 3 x 100 mL). The combined organic solutions were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH}/2 \text{ N NH}_3$ in MeOH 100/20/10), giving the desired product as a colorless oil (241 mg, 18%): $^1\text{H NMR}$ δ 1.18 (s, 3 H), 1.61 (p, $J = 7 \text{ Hz}$, 2 H), 1.75 (m, 2 H), 2.10 (m, 2 H), 2.33 (t, $J = 7 \text{ Hz}$, 2 H), 2.40 (m, 2 H), 2.45 (m, 2 H), 2.72 (t, $J = 6 \text{ Hz}$, 2 H), 3.02 (br s, 2 H), 7.14 (m, 1 H), 7.30 (m, 4 H); $^{13}\text{C NMR}$ δ 30.28, 36.78, 37.64, 41.51, 50.96, 57.51, 126.16, 126.40, 128.91, 149.20.

Preparation of

3-[4-(4-Fluorophenyl)piperidin-1-yl]propylamine

4-(4-FLUOROPHENYL)PIPERIDINE HYDROCHLORIDE: To a solution of 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (10 g) in methanol (200 mL) was added 10% palladium on charcoal (0.5 g) and the mixture was hydrogenated at 50 psi for 3 h. The catalyst was removed by filtration and solvent was evaporated, leaving the product (10.0 g) as a white powder, which was used in the next step without purification. The product appeared to be pure based on $^1\text{H NMR}$ and TLC analysis. $^1\text{H NMR}$ δ 1.95-2.03 (br d, 2H), 2.14-2.29 (m, 2H), 2.70-2.80 (m, 1H), 2.91-3.07 (br q, 2H), 3.60-3.64 (br d, 2H), 6.96-7.03 (m, 2H), 7.19-7.22 (m, 2H), 9.60 (br s, 1H), 9.71 (br s, 1H).

4-(4-FLUOROPHENYL)PIPERIDINE: mp $^{\circ}\text{C}$; $^1\text{H NMR}$ δ 1.51-1.66 (m, 2H), 1.80 (d, $J=7.2 \text{ Hz}$, 2H), 2.53-2.64 (m, 1H), 2.67-2.77 (m, 2H), 3.17 (d, $J=12.0 \text{ Hz}$, 2H), 6.94-7.03 (m, 2H), 7.13-7.21 (m, 2H).

Anal. Calcd. For $\text{C}_{11}\text{H}_{14}\text{NF} + \text{C}_4\text{H}_4\text{O}_4$: C, 58.70; H, 5.83; N, 4.18.

-122-

Found: C, 58.72; H, 5.84; N, 3.98.

3-[4-(4-FLUOROPHENYL)PIPERIDIN-1-YL]PROPYLPHTHALIMIDE: A mixture of 4-(4-fluorophenyl)piperidine hydrochloride (5.08 g, 23.2 mmol), 3-bromopropylphthalimide (6.22 g, 23.2 mmol), and potassium carbonate (15 g) in DMF (100 mL) was stirred at 95-100 °C for 12 h. About 80% of the solvent was evaporated under reduced pressure. The residue was diluted with ethyl acetate (200 mL) and washed with brine (3 X 100 mL) and dried (Na₂SO₄). The solvent was evaporated from the ethyl acetate solution and the residue was purified by column chromatography (1/1 hexane-ethyl acetate to 100% ethyl acetate), giving crude product (7.50 g, 88%). This crude product was crystallized from isopropanol, giving a white crystalline solid (4.50 g, 1st crop). This material was used in the next step. Concentration of the mother liquor and cooling gave the second crop of desired product (1.0 g). ¹H NMR δ 1.43-1.52 (m, 2H), 1.67-1.75 (m, 2H), 1.80-1.96 (m, 4H), 2.33-2.46 (m, 3H), 2.94-2.99 (br d, 2H), 3.78 (t, J=7 Hz, 2H), 6.90-7.04 (m, 4H), 7.70-7.74 (m, 2H), 7.84-7.87 (m, 2H).

3-[4-(4-FLUOROPHENYL)PIPERIDIN-1-YL]PROPYLAMINE: Hydrazine (4 mL) was added to a solution of 3-[4-(4-fluorophenyl)piperidin-1-yl]propylphthalimide (4.50 g, 12.3 mmol) in methanol (200 mL), and the mixture was stirred at reflux for 8 h. The solution was cooled to room temperature, and the resulting white solid which formed was filtered and washed with methanol (20 mL). The solvent was evaporated from the filtrate and residue was dried under vacuum for 4 h. The crude product was dissolved in 50 mL of chloroform, stirred for 1 h, and filtered. The white solid was washed with additional chloroform (20 mL), the solvent was evaporated from the

-123-

combined filtrates to leave the crude product as an oil.
The oil was purified by column chromatography
(dichloromethane / methanol / 2 M ammonia in methanol,
10/3/1), giving the desired product (2.70 g, 93%). ^1H NMR

5 δ 1.60-1.83 (m, 6H), 1.96-2.07 (m, 4H), 2.40-2.55 (m,
3H), 2.70-2.85 (br t, 2H), 3.03-3.07 (br d, 2H),
6.93-7.00 (m, 2H), 7.14-7.20 (m, 2H).

4-(4-METHYL-4-(3,5-DIMETHYLPHENYL)PIPERIDINE:

10 hygroscopic; ^1H NMR δ 1.20 (s, 3H), 1.74-1.80 (m, 2H),
2.08-2.16 (m, 2H), 2.30 (s, 6H), 2.50-2.56 (m, 2H),
2.64-2.68 (m, 2H), 2.97-3.04 (m, 1H), 6.87 (s, 1H), 6.94
(s, 2H).

Piperidine Side Chain Intermediates**TERT-BUTYL 4-[[(TRIFLUOROMETHYL) SULFONYL] OXY]-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE:**

- 5 n-Butyl lithium (17.6 mL, 44.2 mmol, 2.5 M in hexanes) was added to a solution of diisopropyl amine (96.2 mL, 44.2 mmol) in 40 mL of dry THF at 0 °C and stirred for 20 minutes. The reaction mixture was cooled to -78 °C and
- 10 tert-butyl 4-oxo-1-piperidinecarboxylate (Aldrich Chemical Company, 40.0 mmol) in THF (40 mL) was added dropwise to the reaction mixture and stirred for 30 minutes. Tf₂NPh (42.0 mmol, 15.0 g) in THF (40 mL) was added dropwise to the reaction mixture and stirred at °C overnight. The reaction mixture was concentrated in
- 15 vacuo, re-dissolved in hexanes:EtOAc (9:1), passed through a plug of alumina and the alumina plug was washed with hexanes:EtOAc (9:1). The combined extracts were concentrated to yield 16.5 g of the desired product that was contaminated with some starting Tf₂NPh.
- 20 ¹H NMR (400 MHz, CDCl₃) δ 5.77 (s, 1 H), 4.05 (dm, 2 H, J=3.0 Hz), 3.63 (t, 2 H, J=5.7 Hz), 2.45 (m, 2 H), 1.47 (s, 9 H).

TERT-BUTYL 4-[3-(AMINO) PHENYL]-1,2,3,6-TETRAHYDRO-1-PYRIDINECARBOXYLATE:

- 25 A mixture of 2 M aqueous Na₂CO₃ solution (4.2 mL), tert-butyl 4-[[(trifluoromethyl) sulfonyl] oxy]-1,2,3,6-tetrahydro-1-pyridine-carboxylate (0.500 g, 1.51 mmol), 3-aminophenylboronic acid hemisulfate (0.393 g, 2.11 mmol), lithium chloride (0.191 g, 4.50 mmol) and
- 30 tetrakis-triphenylphosphine palladium (0) (0.080 g, 0.075 mmol) in dimethoxyethane (5 mL) was heated at reflux temperature for 3 hours, under an inert

atmosphere (an initial degassing of the mixture is recommended to prevent the formation of triphenylphosphine oxide). The organic layer of the cooled reaction mixture was separated and the aqueous layer was washed with ethyl acetate (3X). The combined organic extracts were dried and concentrated in vacuo. The crude product was chromatographed (silica, hexanes:EtOAc:dichloromethane (6:1:1) with 1% added isopropylamine to protect the BOC group from hydrolysis) to give 0.330 g of the desired product in 81% yield:

^1H NMR (400 MHz, CDCl_3) δ 7.12 (t, 1H, $J = 7.60$ Hz), 6.78 (d, 1H, $J = 8.4$ Hz), 6.69 (t, 1H, $J = 2.0$ Hz), 6.59 (dd, 1H, $J = 2.2, 8.0$ Hz), 6.01 (m, 1H), 4.10-4.01 (d, 2H, $J = 2.40$ Hz), 3.61 (t, 2H, $J = 5.6$ Hz), 2.52-2.46 (m, 2H), 1.49 (s, 9H); ESMS m/e : 275.2 ($M + H$) $^+$.
Anal. Calc. for $\text{C}_{16}\text{H}_{24}\text{N}_2\text{O}_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.78; H, 7.80; N, 9.92

TERT-BUTYL 4-[3-(AMINO)PHENYL]-1-PIPERIDINECARBOXYLATE
A mixture of 3.10 g of tert-butyl 4-(3-aminophenyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (11.3 mmol) and 1.0 g of 10% Pd/C in 200 mL of ethanol was hydrogenated at room temperature using the balloon method for 2 days. The reaction mixture was filtered and washed with ethanol. The combined ethanol extracts were concentrated in vacuo and the residue was chromatographed on silica (dichloromethane: methanol 95:5 with 1% isopropylamine added to protect the BOC group from hydrolysis) to give 2.63 g of the desired product (84%).

**TERT-BUTYL 4-(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-
PYRIDINECARBOXYLATE**

¹H NMR (400 MHz, CHCl₃) δ 8.23 (s, 1H), 8.11 (d, 1H, J=8.0 Hz), 7.69 (d, 1H, J=8.0 Hz), 7.51 (t, 1H, J=8.0 Hz), 6.20 (m, 1H), 4.17-4.08 (m, 2H), 3.67 (t, 2H, J=5.6 Hz), 2.61-2.52 (m, 2H), 1.50 (s, 9H); ESMS m/e : 249.1 (M + H - C₄H₈)⁺.

10 **1,2,3,6-TETRAHYDRO-4-(3-NITROPHENYL)PYRIDINE:** Into a stirred solution of 5.00 g (16.0 mmol) of tert-butyl 1,2,3,6-tetrahydro-4-(3-nitrophenyl)pyridine-1-carboxylate in 100 ml of 1,4-dioxane at 0°C was bubbled HCl gas for 10 minutes. The reaction mixture was
15 allowed to warm to room temperature and the bubbling of the HCl gas was continued for an additional 1 hour. The solvent was removed in vacuo, the residue was dissolved in 50 mL of water and was neutralized by the addition of KOH pellets. The aqueous solution was extracted with 3
20 X 80 mL of dichloromethane and the combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo. The residue was purified by column chromatography (silica, 9 : 1, dichloromethane : methanol + 1% isopropyl amine) to afford 2.85 g (87.5%
25 yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (s, 1H), 8.09 (d, 1H, J=8.4 Hz), 7.71 (d, 1H, J=8.0 Hz), 7.49 (t, 1H, J=8.0 Hz), 6.35-6.25 (m, 1H), 3.58 (apparent q, 2H, J=3.0 Hz), 3.14 (t, 2H, J=5.6 Hz), 2.54-2.46 (m, 2H).

30

TERT-BUTYL 3-(4-(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIDINYL) PROPYLCARBAMATE: A mixture of 2.80 g (14.0 mmol) of 1,2,3,6-tetrahydro-4-(3-nitrophenyl)pyridine,

3.60 g (15.0 mmol) of *tert*-butyl N-(3-bromopropyl)carbamate, 11.6 g (84.0 mmol) of K₂CO₃, 14.6 mL (84.0 mmol) of diisopropylethylamine and 0.78 g (2.00 mmol) of tetrabutylammonium iodide in 250 mL of 1,4-dioxane was heated at reflux temperature for 14 hours. The reaction mixture was filtered and the filtrate was dried (MgSO₄), concentrated *in vacuo* and the residue was purified by column chromatography (silica, 9:1, dichloromethane: methanol + 1% isopropyl amine) to afford 4.35 g (85.7% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (t, 1H, J=1.9 Hz), 8.09 (dd, 1H, J=1.9, 8.0 Hz), 7.70 (apparent d, 1H, J=8.0 Hz), 7.49 (t, 1H, J=8.0 Hz), 6.23 (m, 1H), 3.29-3.18 (m, 4H), 2.75 (t, 2H, J=5.6 Hz), 2.64-2.54 (m, 4H), 1.82-1.70 (m, 2H), 1.44 (s, 9H); ESMS m/e : 362.2 (M + H)⁺.

3-(4-(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIDINYL)-1-PROPANAMINE: Into a stirred solution of 4.35 (12.0 mmol) of *tert*-butyl 3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)propylcarbamate in 100 mL of 1,4-dioxane at 0°C was bubbled HCl gas for 10 minutes. The reaction mixture was allowed to warm to room temperature and the bubbling was continued for an additional 1 hour. The solvent was removed *in vacuo*, the residue was dissolved in 50 mL of water and was neutralized by the addition of KOH pellets. The aqueous solution was extracted with 3 X 80 mL of dichloromethane, the combined organic extracts were dried (MgSO₄), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 9 : 1 ,dichloromethane : methanol + 1% isopropyl amine) to afford 3.05 g (97.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 8.24 (t, 1H, J=1.8 Hz), 8.09 (dd, 1H, J=1.8, 8.2 Hz),

7.69 (dd, 1H, J=1.8, 8.2 Hz), 7.48 (t, 1H, J=8.2 Hz),
6.24 (m, 1H), 3.21 (d, 2H, J=3.6 Hz), 2.84 (t, 2H, J=6.6
Hz), 2.75 (t, 2H, J=5.8 Hz), 2.64-2.54 (m, 4H), 1.76 (m,
2H); ESMS m/e : 262.2 (M + H)⁺; Anal. Calc. for
5 C₁₄H₁₉N₃O₂ (0.06 CHCl₃): C, 62.90; H, 7.16; N, 15.65.
Found: C, 63.20; H, 7.16; N, 15.65.

METHYL (4S)-3-[(3-[4-(3-AMINOPHENYL)-1-
PIPERIDINYL]PROPYL)AMINO)CARBONYL]-4-(3,4-
10 DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-
TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: A mixture of 3.02 g
(6.33 mmol) 5-methyl 1-(4-nitrophenyl) (6S)-6-(3,4-
difluorophenyl)-4-(methoxymethyl)-2-oxo-3,6-dihydro-
1,5(2H)-pyrimidinedicarboxylate, 1.50 g (5.80 mmol) of
15 3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)-1-
propanamine, 7.94 g (75.5 mmol) of K₂CO₃ and 1.00 mL of
methanol in 200 mL dichloromethane (under argon) was
stirred at room temperature for 1 hour. The reaction
mixture was filtered and concentrated in vacuo. The
20 residue was dissolved in 100 mL of ethyl acetate and
washed 3 X 50 mL of 5% aqueous NaOH solution, the
organic layer was dried (MgSO₄) and concentrated in
vacuo. The residue was dissolved in 100 mL of anhydrous
ethanol containing 0.50 g 10% Pd/C and the reaction
25 mixture was stirred under a hydrogen balloon for 24
hours. The reaction mixture was passed through a column
of Celite 545 filtering agent, washed with ethanol, the
filtrate was dried (MgSO₄) and concentrated in vacuo.
The residue was purified by column chromatography
30 (silica, 9.5 : 0.5, dichloromethane : methanol + 1%
isopropyl amine) to afford 1.65 g (52.0% yield) of the
desired product.

TERT-BUTYL 4-[3-(ISOBUTYRYLAMINO)PHENYL]-3,6-DIHYDRO-1(2H)-PYRIDINECARBOXYLATE: Into a solution of 4.00 g (16.0 mmol) of tert-butyl 4-(3-aminophenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate and 5.60 mL (32.0 mmol) of diisopropylethylamine in 100 mL dichloromethane was slowly added 1.90 mL (19.0 mmol) of isobutyryl chloride. The reaction mixture was stirred at room temperature for 2 hours, washed with water, dried (MgSO₄), and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 50 : 46 : 3 : 1, hexanes : dichloromethane : methanol : isopropyl amine) to afford 2.90 g (52.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 7.69 (s, 1 H), 7.34 (d, 1 H, J=7.8 Hz), 7.27 (t, 1H, J=7.8 Hz), 7.11 (d, 1H, J=7.8 Hz), 6.04 (s, 1H), 4.05 (s, 2H), 3.62 (apparent t, 2 H, J=4.9 Hz), 2.51 (m, 3H), 1.49 (s, 9H), 1.25 (d, 6H, J=7.4 Hz); ESMS *m/e*: 345.5 (M + H)⁺. Anal. Calc. for C₂₀H₂₈N₂O₃+0.175 CHCl₃: C, 66.33; H, 7.77; N, 7.67. Found: C, 66.20; H, 7.41; N, 7.88

20

TERT-BUTYL 4-[3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINECARBOXYLATE: A mixture of 2.90 g (8.40 mmol) of tert-butyl 4-[3-(isobutyrylamino)phenyl]-3,6-dihydro-1(2H)-pyridinecarboxylate and 0.80 g of 10% yield Pd/C in 100 mL of ethanol was stirred under a hydrogen balloon for 24 hours. The reaction mixture was passed through a column of Celite 545 filtering agent, the filtrate was dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 9.5 : 0.5, dichloromethane : methanol + 1% isopropyl amine) to afford 2.40 g (84.0% yield) of the desired product: ¹H NMR (400 MHz, CDCl₃) δ 7.49-7.44 (m, 2H), 7.24 (t, 1H, J=7.6 Hz), 6.93 (d, 1H, J=7.6 Hz),

30

4.20-4.10 (m, 2H), 2.86-2.45 (m, 4H), 1.86-1.75 (m, 4H), 1.48 (s, 9H), 1.24 (d, 6H, $J=6.8$ Hz); ESMS m/e : 345.2 ($M + H$)⁺; Anal. Calc. for $C_{20}H_{30}N_2O_3 + 0.3H_2O$: C, 68.27; H, 8.77; N, 7.96. Found: C, 68.25; H, 8.54; N, 7.84.

5

2-METHYL-N-[3-(4-PIPERIDINYL)PHENYL]PROPANAMIDE: Into a stirred solution of 2.20 (6.50 mmol) of tert-butyl 4-[3-(isobutyrylamino)phenyl]-1-piperidinecarboxylate in 100 ml of 1,4-dioxane at 0 °C was bubbled HCl gas for 10 minutes. The reaction mixture was allowed to warm to room temperature and the bubbling of the HCl gas was continued for 1 hour. The solvent was removed *in vacuo*, the residue was dissolved in 50 mL of water and was neutralized by the addition of KOH pellets. The aqueous solution was extracted with 3 X 80 mL of dichloromethane, the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography (silica, 9 : 1, dichloromethane : methanol + 1% isopropyl amine) to afford 0.700 g (46.0% yield) of the desired product: 1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.40 (d, 1H, $J=7.8$ Hz), 7.24 (t, 1H, $J=7.8$ Hz), 7.00 (d, 1H, $J=7.8$ Hz), 3.23-3.14 (m, 5H), 2.82-2.57 (m, 4H), 1.20 (d, 6H, $J=6.8$ Hz); ESMS m/e : 247.2 ($M + H$)⁺;

25 The hydrochloride salt was used for the combustion analysis: Anal. Calc. for $C_{15}H_{22}N_2O + HCl + 0.15 CHCl_3$: C, 60.51; H, 7.76; N, 9.32. Found: C, 60.57; H, 7.83; N, 8.88.

30 **3-(4-PIPERIDINYL)ANILINE:** 1H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, 1H, $J=7.6$ Hz), 6.62-6.54 (m, 3H), 3.16 (br d, 2H, $J=10.3$ Hz), 2.75 (dt, 2H, $J=2.7, 12.3$ Hz), 2.56 (tt, 1H,

131

J=3.6, 12.3 Hz), 1.81 (br d, 2H, J=12.3 Hz), 1.65 (dq, 2H, J=4.0, 12.3 Hz); ESMS m/e : 177.2 (M + H)⁺.

TERT-BUTYL 4-(4-NITROPHENYL)-3,6-DIHYDRO-1(2H)-

5 **PYRIDINECARBOXYLATE:** To a 25-mL RB flask, equipped with a condensor, was added tert-butyl 4-
{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydro-1(2H)-pyridinecarboxylate (1.0 g), 4-nitrophenylboronic acid (0.71 g), sodium carbonate (0.430 mL of 2M solution),
10 lithium chloride (0.382 g), tetrakis(triphenylphosphine)-palladium (0) (0.173 g) and ethylene glycol dimethyl ether (10 mL). The reaction mixture was flushed with Argon three times, then the reaction mixture was heated to 100 °C for 3 hrs.
15 After cooling to room temperature, the reaction mixture was diluted with methylene chloride (30 mL) and water (30 mL) and the organic layer was separated. The aqueous layer was extracted with methylene chloride (3x20 mL) and the combined organic extracts were washed
20 with sat NH₄Cl (20 mL) and brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by chromatography (6:1=hexane:ethyl acetate with 1% NH₃) to afford the product (0.55 g, 59.9%) as a yellow oil. The compound is not stable at
25 room temperature and should be used as prompt as practical: ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, 2H, J=8.6 Hz), 7.51 (d, 2H, J=8.6 Hz), 6.24 (m, 1H), 4.13 (m, 2H), 3.67 (apparent t, 2H, J=5.5 Hz), 2.55 (m, 2H), 1.49 (s, 9H).

30

4-(4-NITROPHENYL)-1,2,3,6-TETRAHYDROPYRIDINE:

4-(4-Nitrophenyl)-1,2,3,6-tetrahydropyridine was prepared by a similar procedure to that used for the

preparation of 2-methyl-N-[3-(4-piperidinyl)phenyl]propanamide using HCl gas and tert-Butyl 4-(4-Nitrophenyl)-3,6-dihydro-1(2H)-pyridinecarboxylate (130 mg) in dioxane (5.0 mL) at room temperature. The reaction mixture was concentrated in vacuo to give the crude product (69.8 mg) that used in the next reaction without further purification.

10 Dihydropyrimidine Intermediates

3-(3,4,5-TRIFLUOROBENZYLIDENE)-2,4-PENTANEDIONE: A stirring mixture of 3,4,5-trifluorobenzaldehyde (4.20 g, 26.2 mmol), 2,4-pentanedione (2.62 g, 26.2 mmol), piperidine (0.430 g, 5.00 mmol) in benzene (150 mL) was heated at reflux temperature in a Dean-Stark apparatus for 8 h. The benzene was evaporated and the yellow oily residue was used in the next step without further purification.

1-[2-METHOXY-4-METHYL-6-(3,4,5-TRIFLUOROPHENYL)-1,6-DIHYDRO-5-PYRIMIDINYL]ETHANONE: A mixture 3-(3,4,5-trifluorobenzylidene)-2,4-pentanedione (26.2 mmol), O-methylisourea hydrogen sulfate (3.22 g, 39.3 mmol), and NaHCO₃ (6.6 g, 78.6 mmol) in EtOH (400 mL) was stirred and heated at 95-100 °C for 6 h. The mixture was filtered and the solid filter cake was washed with ethanol (100 mL). The solvent was evaporated from the combined filtrates and the crude product was purified by flash column chromatography (EtOAc/hexane, 1/9 to 1/4), to afford the desired product as an oil (2.80 g, 36%).

4-NITROPHENYL 5-ACETYL-2-METHOXY-4-METHYL-6-(3,4,5-TRIFLUOROPHENYL)-1(6H)-PYRIMIDINECARBOXYLATE:

4-Nitrophenyl chloroformate (1.89 g, 9.38 mmol) was added to a solution of 1-[2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-1,6-dihydro-5-pyrimidinyl]ethanone (2.80 g, 9.38 mmol) and pyridine (10 mL) in CH₂Cl₂ (200 mL) at 0-5 °C, and the resulting mixture was allowed to warm to room temperature. After 12 h, the solvent was evaporated and the residue was purified by flash chromatography (dichloromethane/EtOAc, 1/9 to 3/20), to give the desired product as a white powder (4.00 g, 92%).

4-NITROPHENYL 5-ACETYL-4-METHYL-2-OXO-6-(3,4,5-TRIFLUOROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIMIDINECARBOXYLATE:

A solution of 6 N aqueous HCl (4 mL) was added to a well-stirred solution of 4-nitrophenyl 5-acetyl-2-methoxy-4-methyl-6-(3,4,5-trifluorophenyl)-1(6H)-pyrimidinecarboxylate (4.00 g, 8.63 mmol) in THF (100 mL) at 0-5 °C, and the mixture was allowed to warm to room temperature. After 2 h, solvent was evaporated and the product dried under vacuum. The product was obtained as a pure single component and used in the next step without further purification (3.88 g, 100%).

: ¹H NMR (DMSO) δ 10.29 (s, 1H), 8.23 (d, 2H, J=9.1 Hz), 7.51 (d, 2H, J=9.1 Hz), 7.15-7.07 (m, 2H), 6.18 (s, 1H), 2.30 (s, 3H), 2.28 (s, 3H); ESMS m/e: 450.2 (M + H)⁺; Anal. Calc. for C₂₀H₁₄F₃N₃O₆: C, 53.46; H, 3.14; N, 9.35. Found: C, 53.26; H, 3.21; N, 9.35.

BENZYL 2-PROPIONYL-3-(3,4,5-TRIFLUOROPHENYL)-2-PROPENOATE. A solution of benzyl propionylacetate (36.3 g, 176 mmol), 3,4-difluorobenzaldehyde (25.0 g, 176 mmol), piperidine (0.86 mL, 9.0 mmol) and acetic acid (0.49 mL, 9.0 mmol) were heated at reflux temperature with removal of water using a Dean-Stark apparatus for 5h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc. The organic layer was washed with water (100 mL) followed by brine (100 mL) and dried over anhydrous Na₂SO₄. The solvent was evaporated to afford a pale yellow syrup (60.2 g), which was used in the next step without further purification.

BENZYL 6-(3,4-DIFLUOROPHENYL)-4-ETHYL-2-METHOXY-1,6-DIHYDRO-5-PYRIMIDINECARBOXYLATE. A suspension of benzyl 2-propionyl-3-(3,4,5-trifluorophenyl)-2-propenoate (16.0 g, 48.0 mmol), O-methylisourea hydrogen sulfate (16.65 g, 97.02 mmol), NaHCO₃ (16.3 g, 130.2 mmol) in DMF (190 mL) was stirred at 70 °C for 20h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was diluted with EtOAc (300 mL) and then washed with water (4X100 mL), brine (200 mL) and dried over Na₂SO₄. After removal of solvent, the residue was purified by column chromatography (SiO₂, EtOAc/Hexane, 10%-30%) to afford benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1,6-dihydro-5-pyrimidinecarboxylate as a colorless oil (10.6 g, 58% yield). The product was directly used in the next step after ¹H NMR spectroscopy which showed it to be a mixture of amine/imine tautomers.

5-BENZYL 1-(4-NITROPHENYL) 6-(3,4-DIFLUOROPHENYL)-4-ETHYL-2-METHOXY-1,5(6H)-PYRIMIDINEDICARBOXYLATE.

Into a well-stirred solution of benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1,6-dihydro-5-pyrimidinecarboxylate (27.5 g, 68.75 mmol) and pyridine (9.2 mL) in CH₂Cl₂ (300 mL) was added 4-nitrophenyl chloroformate (14.49 g, 82.5 mmol) at room temperature. The reaction mixture was stirred for 4 h and then washed with 10% aqueous KOH solution (2 X 150 mL). The organic layer was separated and dried over Na₂SO₄. The solvent was removed *in vacuo* and the residue was used in the next step without further purification: ¹H NMR (CDCl₃) δ 1.24 (t, J=7.2 Hz, 3H), 2.81-2.98 (m, 3H), 3.97 (s, 3H), 5.14 (AB_q, 2H), 6.28 (s, 3H), 7.03-7.29 (m, 8H), 7.35 (d, J=9.2 Hz, 2H), 8.26 (d, J=9.2 Hz, 2H).

**BENZYL 6-(3,4-DIFLUOROPHENYL)-4-ETHYL-2-METHOXY-1-
([[(1R)-1-PHENYLETHYL]AMINO]CARBONYL)-1,6-DIHYDRO-5-
PYRIMIDINECARBOXYLATE.**

Into a stirred mixture of 5-benzyl 1-(4-nitrophenyl) 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1,5(6H)-pyrimidinedicarboxylate (12.6 g, 22.86 mmol) in THF (150 mL) was added a solution of R-(+)-α-methyl benzylamine (3.53 mL, 27.44 mmol) at room temperature. The stirring was continued for 12 h and the solvent was removed *in vacuo*. The yellow residue was dissolved in chloroform (200 mL) and was washed with 10% K₂CO₃ solution (2 x 30 mL). The organic layer was dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. The resulting mixture of diastereomers was separated by column chromatography over silica gel with 9:1 pet. ether:ether to 4:1 pet. ether:ether. First major product to elute was (+)-benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1-([[(1R)-1-phenylethyl]amino]carbonyl)-1,6-dihydro-5-pyrimidinecarboxylate: Colorless oil, R_f= 0.31 (4:1 pet

ether:ether); wt.= 3.8 g (60% yield); $[\alpha]_D = +267.05$ ($c = 0.76$, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 1.22 (t, $J=7.5$ Hz, 3H), 1.52 (d, $J=6.9$ Hz, 3H), 2.88 (q, $J=6.0$ Hz, 2H), 3.99 (s, 3H), 4.99 (m, 1H), 5.09 (AB_q, 2H), 6.66 (s, 1H), 6.99-7.36 (m, 13H); The second major product to elute was (-)-benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1-(((1R)-1-phenylethyl)amino)carbonyl)-1,6-dihydro-5-pyrimidinecarboxylate: Colorless oil; $R_f = 0.22$ (4:1 pet ether:ether); wt.= 3.2 g (51.2% yield); $[\alpha]_D = -146.89$ ($c = 0.38$, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 1.22 (t, $J=7.2$ Hz, 3H), 1.49 (d, $J=6.6$ Hz, 3H), 2.88 (q, $J=6.0$ Hz, 2H), 3.94 (s, 3H), 5.03 (m, 1H), 5.11 (AB_q, 2H), 6.68 (s, 1H), 6.91-7.34 (m, 13H).

15 **(+)-BENZYL 6-(3,4-DIFLUOROPHENYL)-4-ETHYL-2-METHOXY-1,6-DIHYDRO-5-PYRIMIDINECARBOXYLATE.** Into a stirred solution of (+)-benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1-(((1R)-1-phenylethyl)amino)carbonyl)-1,6-dihydro-5-pyrimidinecarboxylate (17.1 mmol, 9.35 g) in CH_2Cl_2 was added 1,8-diazabicyclo[5,4,0]-undec-7-ene (17.1 mmol, 2.56 mL) and stirring was continued for 16 h at room temperature. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel with 3:1 EtOAc/Hexanes as the eluting system. 5.27 g of the (+)-benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1,6-dihydro-5-pyrimidinecarboxylate was obtained (77% yield).

30 **(+)-5-BENZYL 1-(4-NITROPHENYL) 6-(3,4-DIFLUOROPHENYL)-4-ETHYL-2-METHOXY-1,5(6H)-PYRIMIDINEDICARBOXYLATE.** Into a well-stirred solution of (+)-benzyl 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1,6-dihydro-5-

pyrimidinecarboxylate (6.4 g, 16.0 mmol) and pyridine (1.5 mL) in CH₂Cl₂ (150 mL) was added 4-nitrophenyl chloroformate (3.41 g, 19.2 mmol) at room temperature. The reaction mixture was stirred for 4 h and then it was washed with 10% aqueous KOH solution (2 X 100 mL). The organic layer was separated and dried over Na₂SO₄. The solvent was removed in vacuo. The residue of (+)-5-benzyl 1-(4-nitrophenyl) 6-(3,4-difluorophenyl)-4-ethyl-2-methoxy-1,5(6H)-pyrimidinedicarboxylate was used in the next step without further purification.

a. 2-(4-METHOXYBENZYL)-2-THIOPSEUDOUREA HYDROCHLORIDE.

Into a well-stirred suspension of thiourea (7.6 g, 0.1 mol) in THF (50 mL) at 0 °C, 4-methoxybenzyl chloride (16 g, 0.1 mol) was added in 10 min and the reaction mixture was allowed to warm to room temperature. After 2 hours the reaction mixture was heated to 65 °C and kept at that temperature for 5 hours. The reaction mixture was cooled to room temperature and diluted with diethyl ether (200 mL). The white precipitate that formed was filtered and dried (22.5 g, 96% yield); m. p. 161-163 °C.

b. METHYL 2-((4-NITROPHENYL)METHYLENE)-3-OXOBUTYRATE.

A mixture of 4-nitrobenzaldehyde (15.1 g, 0.1 mol), methyl acetoacetate (12.773 g, 0.11 mol), piperidine (0.41 g, 4.80 mmol), and acetic acid (0.288 g, 4.8 mmol) in 2-propanol (400 mL) was stirred at room temperature for 48 hours. The resulting white solid, methyl 2-((4-nitrophenyl)methylene)-3-oxobutyrates was filtered, washed with 2-propanol (2 X 50 mL) and dried (21.8 g, 93% yield).

c.

1,6-DIHYDRO-5-METHOXYCARBONYL-2-[(4-METHOXYPHENYL)METHYL]THIO]-4-METHYL-6-(4-NITROPHENYL)PYRIMIDINE.

A mixture of methyl 2-[(4-nitrophenyl)methylene]-3-oxobutyr-
5 oxobutyr-ate (8.96 g, 0.04 mol), 2-(4-methoxybenzyl)-2-thiopseudourea hydrochloride (9.28 g, 0.04 mol), and NaOAc (3.28 g, 0.04 mol) in DMF (100 mL) was stirred and heated at 70-75 °C for 4.5 hours. The reaction mixture was cooled to room temperature, poured into ice-water
10 (300 mL) and extracted with EtOAc (2 X 400 mL). The combined EtOAc extracts were washed with 10% NaHCO₃ solution (2 X 60 mL), brine (100 mL), and then dried (MgSO₄). The solvent was evaporated and the crude product was purified by flash column chromatography on
15 silica gel using 10% through 30% EtOAc in hexane as the gradient eluent. The desired product was obtained as an oil, which on trituration with EtOAc/hexane became a yellow solid (11.4 g, 66.7% yield) which was shown by ¹H NMR to be a mixture of tautomers: m.p. 138-139 °C; ¹H NMR
20 (CDCl₃) δ 2.15 (s, 3 H), 3.62 (s, 3 H), 3.72 (s, 3 H), 4.05 and 5.78 (s and d, J=3 Hz, 1 H), 4.08, 4.20 (AB q, J=12.5 Hz, 2 H), 4.21 and 6.40 (s and d, J=3 Hz, 1 H), 6.66 (2 d, J=8.5 Hz, 2 H), 7.08 (2 d, J=8.5 Hz, 2 H), 7.37 (2 d, J=8.8 Hz, 2 H), 8.7 (2 d, J=8.8 Hz, 2 H);
25 Anal. Calcd. for C₂₁H₂₁N₃O₅S: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.02; H, 4.93; N, 9.77.

d. 1,6-DIHYDRO-5-METHOXYCARBONYL-2-[(4-METHOXYPHENYL)METHYL]THIO]-4-METHYL-6-(4-NITROPHENYL)-1-[(4-NITROPHENYL)OXY]CARBONYL]PYRIMIDINE.

30 Into a well-stirred mixture of 1,6-dihydro-5-methoxy carbonyl-2-[(4-methoxyphenyl)methyl]thio]-4-methyl-6-(4-nitrophenyl)pyrimidine (4.50 g, 10.5 mmol), NaHCO₃ (3.69

g, 0.044 mol), CH₂Cl₂ (200 mL), and water (50 mL) at 0-5 °C, 4-nitrophenyl chloroformate (2.40 g, 12.0 mmol) was added over a 5 min period and the reaction mixture was allowed to warm to room temperature. After 10 hours, the TLC analysis of the reaction mixture showed the presence of a small amount of starting pyrimidine, therefore, more 4-nitrophenyl chloroformate (0.65 g, 0.0032 mol) was added and the stirring was continued for an additional 4 hours. The two layers were separated, the CH₂Cl₂ layer was washed with saturated aqueous NaHCO₃ solution (3 X 50 mL), dried (MgSO₄), and the solvent evaporated. The residue was recrystallized from CH₂Cl₂ and hexane to give the product as white crystals (5.50 g, 88.4% yield): m.p. 156-157 °C; ¹H-NMR (CDCl₃) δ 2.53 (s, 3 H), 3.70 (s, 3 H), 3.81 (s, 3 H), 4.06, 4.36 (ABq, J=13.5 Hz, 2 H), 6.30 (s, 1 H), 6.78 (d, J=8.6 Hz, 2 H), 7.17 (d, J=8.6 Hz, 2 H), 7.20 (d, J=8.8 Hz, 2 H), 7.32 (d, J=8.8 Hz, 2 H), 7.97 (d, J=8.8 Hz, 2 H), 8.25 (d, J=8.8 Hz, 2 H); Anal. Calcd. for C₂₈H₂₄N₄O₉S: C, 56.75; H, 4.08; N, 9.45. Found: C, 56.49; H, 4.28; N, 9.25.

a. 6-(BENZOFURAZAN-5-YL)-1,6-DIHYDRO-2-OXO-5-METHOXYCARBONYL-4-BROMOMETHYL-1-[(4-NITROPHENYL-OXY)CARBONYL]PYRIMIDINE.

Into a well-stirred solution of 6-(benzofurazan-5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-nitrophenyl-oxy)carbonyl]pyrimidine (0.310 mmol, 0.140 g) in 1.5 mL of chloroform was added a solution of bromine (0.310 mmol, 0.020 mL) in 1.5 mL of chloroform at 0 °C and the solution was allowed to attain room temperature over 1.5 h. The solvent was removed in vacuo and the residue was again dissolved in CHCl₃ (10 mL) and washed with brine. The organic layer was

separated, dried over Na_2SO_4 , filtered and the solvent was removed in vacuo to obtain 0.15 g (88% yield) of 6-(benzofurazan-5-yl)-1,6-dihydro-2-oxo-5-methoxycarbonyl-4-bromomethyl-1-[(4-nitrophenyl-oxy)carbonyl]pyrimidine as a yellow foam. The crude product was used in the next step without purification. ^1H NMR (CDCl_3) δ 3.79 (s, 3 H), 4.72 (ABq, 2 H), 6.47 (s, 1 H), 7.37 (d, $J=9.1$ Hz, 2 H), 7.51 (d, $J=7.8$ Hz, 1 H), 7.80 (s, 1 H), 7.92 (d, $J=9.1$ Hz, 1 H), 8.30 (d, $J=9.1$ Hz, 2 H).

c. 4-NITROPHENYL 4-(2,1,3-BENZOXADIAZOL-5-YL)-2,5-DIOXO-1,2,5,7-TETRAHYDROFURO[3,4-D]PYRIMIDINE-3(4H)-CARBOXYLATE.

6-(3,4-Benzofurazan-5-yl)-1,6-dihydro-2-oxo-5-methoxycarbonyl-4-bromomethyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (0.27 mmol, 0.15 g) was heated in oil bath for 3 h (bath temperature 130°C). The brownish-yellow residue thus obtained was washed with CHCl_3 and 4-nitrophenyl 4-(2,1,3-benzoxadiazol-5-yl)-2,5-dioxo-1,2,5,7-tetrahydrofuro[3,4-d]pyrimidine-3(4H)-carboxylate was obtained as an off-white solid which was used in the next step without further purification (crude wt. 0.11 g, 93% yield): ^1H NMR ($\text{DMSO}-d_6$) δ 8.38-7.56 (m, 7H), 6.33 (s, 1H), 5.02 (s, 2H); Anal. Calc. for $\text{C}_{19}\text{H}_{11}\text{N}_5\text{O}_8+2.3\text{H}_2\text{O}$: C, 47.85; H, 3.28; N, 14.63. Found: C, 47.73; H, 2.51; N, 14.77.

5-METHYL 1-(4-NITROPHENYL) 4-(BROMOMETHYL)-6-(3,4-DIFLUOROPHENYL)-2-OXO-3,6-DIHYDRO-1,5(2H)-PYRIMIDINEDICARBOXYLATE: Into a well-stirred solution of 6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-[(4-

nitrophenyloxy)carbonyl]pyrimidine (1.5 mmol, 0.66 g) in 5 mL of chloroform was added a solution of bromine (1.5 mmol, 0.09 mL) in 3 mL of chloroform at 0 °C and the solution was allowed to attain room temperature over 1.5 h. The solvent was removed *in vacuo* and the residue was again dissolved in CHCl₃ (20 mL) and washed with brine. The organic layer was separated, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo* to afford the desired product as a yellow foam, which was used in the next step without purification. ¹H NMR δ 3.75 (s, 3 H), 4.67 (ABq, 2 H), 6.35 (s, 1 H), 7.09-7.19 (m, 4 H), 7.37 (d, J=9.0 Hz, 2 H), 8.27 (d, J=9.0 Hz, 2 H).

4-NITROPHENYL 4-(3,4-DIFLUOROPHENYL)-2,5-DIOXO-1,2,5,7-TETRAHYDROFURO[3,4-D]PYRIMIDINE-3(4H)-CARBOXYLATE.
5-methyl 1-(4-nitrophenyl) 4-(bromomethyl)-6-(3,4-difluorophenyl)-2-oxo-3,6-dihydro-1,5(2H)-pyrimidinedicarboxylate (1.5 mmol, 0.81 g) was heated in an oil bath for 3 h (bath temperature 130 °C). The brown residue thus obtained was washed with CHCl₃ and the desired product was obtained as a pale brown solid which was used in the next step without further purification (crude wt. 0.51 g): ¹H NMR (DMSO-d₆) δ 4.94 (br s, 2 H), 6.08 (s, 1 H), 7.20-7.43 (m, 4 H), 8.35 (d, J=10.2 Hz, 2 H).

4-NITROPHENYL 4-(1,3-BENZODIOXOL-5-YL)-2,5-DIOXOHEXAHYDROFURO[3,4-D]PYRIMIDINE-3(4H)-CARBOXYLATE: ¹H NMR (DMSO) δ 11.35 (s, 1H), 8.16 (d, 2H, J=9.5 Hz), 7.32 (d, 2H, J=8.9 Hz), 6.81-6.65 (m, 3H), 5.88 (s, 1H), 4.85 (ABq, 2H); ESMS m/e : 440.1 (M + H)⁺; Anal. Calc. for C₂₀H₁₅N₃O₉+1.5H₂O: C, 51.29; H, 3.87; N, 8.97. Found: C, 51.38; H, 2.85; N, 8.73.

5-METHYL 1-(4-NITROPHENYL) (6S)-6-(3,4-DIFLUOROPHENYL)-
4-METHYL-2-OXO-3,6-DIHYDRO-1,5(2H)-

5 PYRIMIDINEDICARBOXYLATE: ^1H NMR (400 MHz, CDCl_3) δ 8.29
(d, 2H, $J=9.1$ Hz), 7.36 (d, 2H, $J=8.9$ Hz), 7.25-7.11 (m,
3H), 6.37 (s, 1H), 3.75 (s, 3H), 2.46 (s, 3H); ESMS m/e :
448.1 ($M + H$) $^+$; Anal. Calc. for $\text{C}_{20}\text{H}_{15}\text{F}_2\text{N}_3\text{O}_7$: C, 53.70; H,
3.38; N, 9.39. Found: C, 53.35; H, 3.36; N, 9.27.

-143-

BENZYL

4-[[(TERT-BUTOXYCARBONYL)AMINO]METHYL]CYCLOHEXYLCARBAMATE
: Oxalyl chloride (1.1 equivalents) was added dropwise to
5 a mixture of 4-[[(tert-butoxycarbonyl)-amino]methyl]-
cyclohexanecarboxylic acid (1 equivalent, Maybridge) in
toluene. The reaction mixture was stirred at room
temperature for 2-6 h. The solvent was removed in vacuo,
the residue was dissolved in acetone and the resulting
10 mixture was added dropwise to an aqueous solution of
sodium azide (1.2 equivalents) at a rate such as to
maintain a temperature of 10-15 °C. After the completion
of the reaction, the reaction mixture was extracted with
ethyl acetate, the combined extracts were dried and
15 concentrated in vacuo. The residue was dissolved in
acetone and added slowly to warm (60 °C) benzene. After
the completion of the reaction, benzyl alcohol was added
to the reaction mixture, stirred for 2 days and the
desired product was isolated (For Typical References,
20 See: G. Schroeter Ber. 1909, 42, 3356; and Allen, C.F.H.;
Bell, A. Org. Syn. Coll. Vol. 3 (1955) 846.).

A solution of benzyl 4-[[(tert-butoxycarbonyl)amino]
methyl]-cyclohexyl carbamate in MeOH containing 10% Pd/C
25 was hydrogenated at 50 psi overnight. The reaction
mixture was filtered through Celite 545 and the Celite
545 was washed with methanol. The combined methanol
extracts were concentrated in vacuo, giving trans-
tert-butyl 4-aminocyclohexylmethylcarbamate (95 %).

30

9H-9-FLUORENYLMETHYL N-[4-(AMINOMETHYL)CYCLOHEXYL]
CARBAMATE: : ¹H NMR δ 8.02 (br, 1 H), 7.33 (m, 5 H), 5.07
(s, 2 H), 3.71 (s, 1 H), 3.40 (br m, 1 H), 2.80 (br m, 2
H), 1.94 (ABq, 4 H), 1.68 (br, 1 H), 1.30-1.00 (m, 5 H).

35

-144-

N1-[4-(AMINOMETHYL)CYCLOHEXYL]-1-NAPHTHAMIDE: HCl in dioxane (10 mL, 4 N) was added to a solution of tert-butyl[4-(1-naphthoyl-amino)cyclohexyl)methylcarbamate (0.350 g) in dichloromethane (20 mL), stirred overnight, concentrated *in vacuo*, giving the desired product: ¹H NMR δ 8.24 (dd, 1 H, J=1.2, 8.7 Hz), 7.85 (dt, 2 H, J=2.7, 9.7 Hz), 7.60-7.30 (m, 4 H), 5.98 (m, 1 H), 4.02 (m, 1 H), 3.80-3.40 (m, 4 H), 2.53 (d, 2 H, J=6.0 Hz), 2.02 (ABq, 4 H), 1.41-1.90 (m, 4 H).

TERT-BUTYL N-(4-[(1-NAPHTHYLCARBONYL)AMINO]-CYCLOHEXYLMETHYL)-CARBAMATE: A mixture of 1-naphthoic acid (1.00 mmol, 0.172 g), DMAP (2.00 mmol, 0.250 g) and ECD (0.383 g, 2.00 mmol) in dry dichloromethane (20 mL) was stirred at room temperature for 0.5 h followed by the addition of tert-butyl(4-amino)cyclohexyl)methylcarbamate amine (1.09 mmol, 0.250 g). The reaction mixture was stirred at room temperature overnight and purified by flash chromatography, giving the desired product as a white solid (0.160 g): ¹H NMR δ 8.29 (dd, 1 H, J=1.8, 9.1 Hz), 7.89 (m, 2 H), 7.60-7.40 (m, 4 H), 5.85 (br d, 1 H, J=6.3 Hz), 4.65 (m, 1 H), 4.04 (m, 1 H), 3.02 (t, 1 H, J=6.3 Hz), 2.05 (ABq, 4 H), 1.62 (m, 2 H), 1.46 (s, 9 H), 1.40-1.10 (m, 4 H).

4-ACETYL-1-(3-AMINOPROPYL)-4-PHENYLPYPERIDINE: A solution of 4-Acetyl-4-phenylpyperidine (7, 1.53 g, 7.50 mmol), 3-bromo-propylamine hydrobromide (1.64 g, 7.50 mmol) and potassium carbonate (1.24 g, 9.00 mmol) was stirred in refluxing 1,4-dioxane (50 mL) for 12 h. After removal of dioxane, water (50 mL) was added and the pH was adjusted to 11-12 by addition of 1 N aqueous NaOH. The mixture was extracted with CH₂Cl₂ (100 mL + 3 x 50 mL). The combined organic solutions were dried over magnesium

-145-

sulfate and concentrated. The residue was purified by flash chromatography (EtOAc-MeOH-Et₃N 100/40/20), giving the desired product as a colorless oil (780 mg, 40%): ¹H NMR δ 1.56 (p, J = 7 Hz, 2 H), 1.84 (s, 3 H), 1.98 (m, 2 H), 2.15 (br t, J = 12 Hz, 2 H), 2.29 (t, J = 7 Hz, 2 H), 2.41 (br d, J = 12 Hz, 2 H), 2.66 (t, J = 7 Hz, 4 H), 7.18 - 7.30 (m, 5 H); ¹³C NMR δ 26.28, 31.11, 33.43, 41.47, 51.62, 55.31, 57.19, 77.32, 77.74, 78.17, 126.95, 127.69, 129.44, 142.25, 210.15.

For the preparation of benzo-4',5'[H]furanpiperidine refer to W.E.Parham et al, *J. Org. Chem.* (1976) 41, 2268.

TERT-BUTOXY{[3-(BENZO-4',5'[H]FURANPIPERIDIN-1-YL)PROPYL]AMINO}METHANOL: To a stirred solution of the N-[4-(benzo-4',5'[H]furanpiperidine (0.566 g, 3.27 mmol) in dioxane (20 mL), N-(tert-butoxycarbonyl)-3-bromopropylamine (0.772 g, 3.27 mmol) and potassium carbonate (0.904 g, 6.54 mmol) were added and the solution was refluxed for 24 h. The reaction mixture was cooled to room temperature, concentrated and partitioned between chloroform (40 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate/ methanol, 4.5/0.5), giving the desired product as a colorless oil (0.856 g, 79 %); ¹H NMR (1.45 (s, 9 H), 1.63-2.04 (m, 6 H), 2.33-2.52 (m, 4 H), 2.87 (d, J=11.0 Hz, 2 H), 3.2 (br s, 2 H), 5.07 (s, 2 H), 5.6 (br s, 1 H), 7.13-7.28 (m, 4 H).

3-(4-METHYL-4-PHENYL-1-PIPERDINYL)PROPYLAMINE:

Trifluoroacetic acid (1 mL) was added to tert-butoxy{[3-(4-methyl-4-phenyl-1-piperdiny)propyl]-amino}methanol (0.500 g, 1.51 mmol) in dichloromethane (5 mL) and the

-146-

solution was stirred at room temperature for 1 h. The solution was concentrated, neutralized with 10 % KOH solution and extracted with dichloromethane (25 mL). The organic layer was dried over sodium sulfate, filtered and concentrated, giving 0.340 g (98%) of 3-(4-methyl-4-phenyl-1-piperdiny)propylamine which was used without further purification in the subsequent step.

Procedures for the Reaction of the Amine Side Chains with the p-Nitrophenylcarbamate Intermediates:

General Procedure:

An equimolar solution of an amine side chain such as 3-(4-methyl-4-phenyl-1-piperdiny)propylamine and a p-nitrophenylcarbamate intermediate such as 5-methoxycarbonyl-4-methoxymethyl- 1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine and 1-2 equivalents of a base such as diisopropylethylamine in dichloromethane were stirred at room temperature overnight. The reaction mixture was concentrated and purified by flash chromatography, giving the desired product. In case of 2-methoxy intermediates, conversion to the oxo derivatives was accomplished by treatment of the 2-methoxy product with HCl in dioxane.

2-OXO-3-{SPIRO[1H-INDANE-1,4'-PIPERIDINE]PROPYLAMINE (0.0319 g, 0.123 mmol) was added to (±)-6-(3,4-difluorophenyl)-1,6-dihydro- 2-methoxy-5-methoxycarbonyl-4-ethyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.052 g, 0.112 mmol) in dry dichloromethane (10 mL) and the solution was stirred at room temperature for 24 h. The reaction mixture was stirred for another 1 h after addition of 6 N HCl (2 mL). After neutralization with aqueous 10% KOH solution, the reaction mixture was

-147-

extracted into dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/ MeOH, 4.5/0.5), giving of the
5 desired product (0.040 g) as a syrup.

1 N HCl in ether (5 mL) was added to the free base (0.040 g, 0.072 mmol) in dichloromethane (4 mL) and the solution was concentrated under reduced pressure. The crude
10 product was recrystallized from ether, giving the desired compound (0.042 g, 99 %) as a pale yellow solid; mp 178-182 °C; Anal. Calcd. for $C_{29}H_{34}F_2N_4O_5Cl_2 + 0.6 H_2O$: C, 57.87; H, 5.73, N 9.31. Found: C, 58.11; H 5.90; N 8.95.

15 General Procedure for the reaction of the piperidines and piperazines with 1-(3-bromo-propylcarbamoyl)-6-(3,4-difluoro-phenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5-carboxylic acid methyl ester:

20 The amine (0.15 mmol) was added to a solution of 1-(3-bromo- propylcarbamoyl)-6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-di-hydropyrimidine-5-carboxylic acid methyl ester (43.0 mg, 0.100 mmol) in anhydrous acetone (10 mL), followed by $NaHCO_3$ (41 mg, 0.3 mmol) and KI (16
25 mg, 0.1 mmol). The resulting suspension was heated to reflux for 10 h and then cooled to room temperature. The solvent was removed in vacuo and the residue was purified by flash column chromatography (EtOAc, followed by EtOAc/MeOH, 9/1). The product was then dissolved in 2 mL
30 of chloroform, acetone or EtOAc and HCl in Et_2O (1 M, 0.5 mL) was added at room temperature. The solvent was removed in vacuo, giving the desired compound as an HCl salt.

35

-148-

Example 1

(-)-1,2,3,6-TETRAHYDRO-1-{N-[4-(3,-ACETAMIDO)-PHENYL-
PIPERIDIN-1- YL]PROPYL}CARBOXAMIDO-4-METHOXYMETHYL-6-
(3,4- DIFLUORO-PHENYL)-2- OXOPYRIMIDINE-5-CARBOXYLIC ACID
5 METHYL ESTER: ESMS, 612.25 (M+1); ¹H NMR δ 1.76-1.87 (m,
6H), 2.03-2.13 (m, 2H), 2.18 (s, 3H), 2.49 (t, J=6.9 Hz,
3H), 3.10 (d, J=11.1 Hz, 2H), 3.30-3.42 (m, 2H), 3.45 (s,
3H), 3.71 (s, 3H), 4.68 (s, 2H), 6.68 (s, 1H), 6.96 (d,
J=7.5 Hz, 1H), 7.04-7.11 (m, 2H), 7.16-7.26 (m, 2H), 7.34
10 (d, J=6.3 Hz, 1H), 7.45 (s, 1H), 7.94 (s, 1H), 8.98 (t,
J=5.4 Hz, 1H).

Example 2

15 METHYL 3-[(3-4-[3-(ACETYLAMINO)PHENYL]-1,2,3,6-
TETRAHYDRO-1-PYR-IDINYLPYR-AMINO]CARBONYL-4-(3,4-
DIFLUOROPHENYL)-6-(METHOXY-METHYL)-2-EXO-1,2,3,4-
TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: ¹H NMR δ 8.90 (t, 1 H,
J=3.6 Hz), 7.75 (s, 1 H), 7.50-7.00 (m, 8 H), 6.68 (s, 1
20 H), 6.03 (br s, 1 H), 4.67 (s, 2 H), 3.71 (s, 3 H), 3.47
(s, 3 H), 3.38 (ABm, 2 H), 3.16 (m, 2 H), 2.71 (t, 2 H, J
=5.4 Hz), 2.56 (m, 4 H), 2.35-1.90 (br, 2 H), 2.17 (s, 3
H), 1.82 (p, 2 H, J=7.2 Hz); ESMS, 612.25 (M+1).

Example 3

25 (1)-1,2,3,6-TETRAHYDRO-1-{N-[3-(4-O-ACETYL)-4-PHENYLPYR-
IDIN-1- YL]PROPYL}CARBOXAMIDO-5-METHOXYCARBONYL-
4-METHOXYMETHYL-6-(3,4- DIFLUOROPHENYL)-2-OXOPYRIMIDINE:
4-Acetyl-1-(3-aminopropyl)- 4-phenylpiperidine (190 mg,
30 0.687 mmol) was added to a stirring solution of 5-methoxy
carbonyl-4-methoxymethyl- 1,2,3,6-tetra-hydro-2-oxo-
6-(3,4-difluorophenyl)-1-[(4-nitrophenoxy)carbon-
yl]pyrimidine (281 mg, 0.573 mmol) in dry
dichloromethane (3 mL) and THF (4 mL). The reaction

-149-

mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with aqueous 6 N HCl. The reaction mixture was concentrated to a small volume, partitioned between dichloromethane and water (100 mL each), the mixture was adjusted to pH 8 by addition of Na_2CO_3 , the layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and the product was chromatographed, giving the desired product. The HCl salt was prepared by the addition of 1 N HCl in ether to a solution of the product in CH_2Cl_2 . The precipitated salt was filtered, washed with ether and dried *in vacuo*, giving (1)-1,2,3,6-tetrahydro-1-{N-[3-(4-O-acetyl)-4-phenylpiperidin-1-yl]propyl}carboxamido-5-methoxycarbonyl-4-methoxymethyl-6-(3,4-difluorophenyl)-2-oxopyrimidine (170 mg, 47%) as the hydrochloride salt: ($\text{C}_{31}\text{H}_{36}\text{N}_4\text{F}_2\text{O}_7 + \text{HCl} + 0.6 \text{ CH}_2\text{Cl}_2$); mp 82-84 °C.

Example 4

Benzyl ester precursor to the product of Example 4:
(+)-1,2,3,6-TETRAHYDRO-1-{N-[4-(BENZO-4',5' (H) FURAN) PIPERIDIN-1-YL] PROPYL}-CARBOXAMIDO-4-ETHYL-6-(3,4-DIFLUOROPHENYL)-2-EXO- PYRIMIDINE-5- CARBOXYLIC ACID
PHENYLMETHYL ESTER: ^1H NMR δ 7.60-7.00 (m, 12 H), 6.85 (br, 1 H), 6.62 (s, 1 H), 5.10 (ABq, 2 H), 5.67 (s, 2 H), 4.03 (br, 1 H), 4.01 (s, 3 H), 3.40 (apparent q, 2 H, $J=6.8$ Hz), 3.20-1.60 (m, 12 H), 2.86 (q, 2 H, $J=2.5$ Hz), 1.19 (t, 3 H, $J=7.5$ Hz).

30

(+)-1,2,3,6-TETRAHYDRO-1-{N-[4-(BENZO-4',5' (H) FURAN) PIPERIDIN-1-YL] PROPYL}-CARBOXAMIDO-4-ETHYL-6-(3,4-DIFLUOROPHENYL)-2-EXO- PYRIMIDINE-5 CARBOXYLIC ACID
HYDROCHLORIDE: ^1H NMR δ 8.95 (br s, 1 H), 8.22 (br s, 1 H),

-150-

7.40-6.95 (m, 7 H), 6.95 (s, 1 H), 6.63 (s, 1 H),
5.10-4.95 (m, 2 H), 3.40-3.20 (m, 4 H), 3.10-2.80 (m, 4
H), 2.55-2.20 (m, 1 H), 2.15 (m, 1 H), 1.85 (m, 2 H),
1.55-1.30 (m, 4 H), 1.20 (t, 3 H, $J=7.6$ Hz); Anal. Calc.
5 For $C_{29}H_{32}N_4O_5F_2 + HCl + 1.5 H_2O$: C, 56.36; H, 5.87; N,
8.06. Found: C, 56.72; H, 6.11; N, 7.61.

Example 5

1,2,3,4-TETRAHYDRO-1-OXO-2-NAPHTHACETIC ACID METHYL
10 ESTER: Under argon, α -tetralone (5.00 g, 34.2 mmol) in
dry THF (300 mL) was treated with LDA in THF (2 M, 18.8
mL) at -78°C . The solution was stirred at -78°C for 1
h. Methyl bromoacetate (15.7 g, 0.103 mole) was then
15 added to the solution, the mixture was stirred overnight
and allowed to warm to room temperature. The solvent was
evaporated and the residue was dissolved into $CHCl_3$ (300
mL), washed with water and saturated brine, and then
dried over Na_2SO_4 . After filtration and removal of
solvent, the residue was vacuum distilled. The product,
20 a colorless oil (7.21 g, 96.5%) was collected at $180^\circ\text{C}/1$
mm Hg; ^1H NMR (400 Mhz) δ 1.98 (m, 1H), 2.25 (m, 1H), 2.44
(m, 1H), 2.90-3.20 (m, 4H), 3.73 (s, 3H), 7.10-8.10 (m,
4H); EI mass spectrum M^+ at m/z 218.

25 1-HYDROXY-2-(2-HYDROXYETHYL)-1,2,3,4-TETRAHYDRONAPHTHALEN
E: A solution of 1,2,3,4-tetrahydro-1-oxo-naphthacetic
acid methyl ester (6.15 g, 28.2 mmol) in THF (150 mL) was
treated with $LiAlH_4$ (2.82 g, 70.5 mmol) and then the
reaction mixture was heated at reflux temperature for 5
30 h. The suspension was cooled to 0°C and quenched by
addition of solid $Na_2SO_4 \cdot 10 H_2O$. The mixture was stirred
at room temperature for 4 hrs. The solid was removed by
filtration and concentration of the filtrate in vacuo
gave a yellow oil (5.33 g, 98.3%); ^1H NMR indicated the

-151-

formation of an isomeric mixture. EI mass spectrum M+ at m/z 192. The mixture was directly used in next reaction without further purification.

5 2-(2-HYDROXYETHYL)-1,2,3,4-TETRAHYDRO-1-OXO-NAPHTHALENE:

A solution of isomeric mixture of 1-hydroxyl-2-(2-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene (3.00 g, 15.6 mmol) in CH₂Cl₂ (100 mL) was treated with MnO₂ (20.4 g, 0.234 mole). The suspension was stirred at room
10 temperature for 16 h and the solids were removed by filtration. Concentration of the filtrate in vacuo gave a brown oil, which was further purified by flash chromatography (MeOH/ CHCl₃ , 5/95), giving a yellow oil (2.00 g, 67.4%): ¹H NMR δ 1.76 (m, 1H), 1.98 (m, 1H), 2.21
15 (m, 2H), 2.57 (br, 1H), 2.70 (m, 2H), 3.20 (m, 2H), 3.81 (m, 2H), 7.00-8.20 (m, 4H); CI mass spectrum (M+1)+ at m/z 191.

20 2-(2-BROMOETHYL)-1,2,3,4-TETRAHYDRO-1-OXONAPHTHALENE: A solution of 2-(2-hydroxyethyl)-1,2,3,4-tetrahydro-1-oxo-naphthalene (2.00 g, 10.5 mmol) in CH₂Cl₂ (100 mL) was treated with PBr₃ (948 mg, 3.50 mmol) at 0 °C. The mixture was stirred at room temperature for 72 h and then poured onto 100 g of ice. The organic layer was
25 separated, washed with aqueous 10% K₂CO₃ solution, H₂O, saturated NaCl and dried over Na₂SO₄. After filtration and removal of the solvent, the residue was purified by chromatography (EtOAc/hexane, 1/10), giving a yellow oil (1.18 g, 44.4%); ¹H NMR δ 1.49 (m, 2 H), 2.24 (m, 1H),
30 2.60 (m, 1H), 2.75 (m, 1H), 3.03 (m, 2H), 3.64 (m, 2H), 7.10-8.10 (m, 4H); EIMS M+ m/z 223, M/M+2=1:1.

2-[2-(4-BENZAMINO-1-PIPERIDYL)ETHYL]-1,2,3,4-TETRAHYDRO-1-OXO-NAPHTHALENE: A mixture of 2-(2-bromoethyl)-

-152-

1,2,3,4-tetrahydro-1-oxonaphthalene (1.18 g, 4.66 mmol),
4-benzamidopiperidine (952 mg, 4.66 mmol) and K_2CO_3 (1.29
g, 9.32 mmol) in acetone (200 mL) was stirred at room
temperature for 48 h. The solids were removed by
5 filtration. Concentration of filtrate in vacuo gave a
yellow solid which was purified by chromatography (MeOH:
CHCl₃, 5/95). The product was recrystallized from an
EtOAc/hexane mixture, giving a white powder (268 mg,
15.3%); mp 158-159 °C; ¹H NMR δ 1.53 (m, 2H), 1.67 (m, 1H),
10 1.91 (m, 1H), 2.02 (m, 2H), 2.21 (m, 4H), 2.50 (m, 3H),
2.95 (m, 4H), 4.01 (m, 1H), 5.95 (d, J=8.0 Hz, 1H),
7.20-8.10 (m, 9H); CI MS (M+1) +m/z 377; Anal. Calcd for
C₂₄H₂₈N₂O₂: C, 76.55; H, 7.51; N, 7.44. Found: C, 76.28; H,
7.46; N, 7.37.

15

Example 6**METHYL**

4-(2,1,3-BENZOXADIAZOL-5-YL)-3-[(1-[4-(DIBUTYLAMINO)-
BENZYL]-4-PIPERIDYLMETHYL)AMINO]CARBONYL-6-METHYL-2-OXO-1
20 ,2,3,4- TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: ¹H NMR δ 7.72
(dd, 1 H, J=0.6, 9.6 Hz), 7.70-7.50 (m, 2 H), 7.11 (d, 2
H, J=8.7 Hz), 6.59 (d, 2 H, J=8.7 Hz), 5.90 (s, 1 H),
3.94 (s, 3 H), 3.63 (s, 2H), 3.24 (t, 4 H, J=7.8 Hz),
2.80 (m, 2 H), 2.49 (d, 2 H, J=6.3 Hz), 2.38 (s, 3 H),
25 2.90-1.00 (m, 5 H), 1.54 (p, 4 H, J= 7.8 Hz), 1.35
(sextet, 4 H, J=7.8 Hz), 0.94 (t, 6 H, J=7.8 Hz).

Example 7

(+)-1,2,3,6-TETRAHYDRO-1-(N-[4-(N'-ETHYL)-N-BENZIMIDAZOLY
30 L- PIPERIDIN-1YL]PROPYL]CARBOXAMIDO-4-METHYL-6-(3,4-
DIFLUOROPHENYL)- 2-OXOPYRIMIDINE HYDROCHLORIDE: ¹H NMR δ
8.95 (t, 1 H, J=3.6 Hz), 7.61 (b, 1 H), 7.60-6.95 (m, 7
H), 6.69 (s, 1 H), 4.36 (m, 1 H), 3.94 (q, 2 H, J=7.2
Hz), 3.72 (s, 3 H), 3.42 (ABm, 4 H), 3.30 (m, 2 H, 4.76

-153-

(m, 4 H), 2.43 (s, 3 H), 2.13 (m, 2 H), 1.77 (m, 4 H),
1.33 (t, 3 H, J=7.2 Hz).

Example 8

5 6-(BENZOFURAZAN-5-YL)-1,2,3,6-TETRAHYDRO-5-METHOXYCARBONYL-
L-4-METHYL-2-OXO-1-{N-[3-(4-PHENYLPYPERIDIN-1-YL)PROPYL]}
CARBOXAMIDO-PYRIMIDINE: A solution of 6-(benzofurazan-
5-yl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-
4-methyl-1-{N-[3-(4-phenylpiperidin-1-yl)propyl]}
10 carboxamidopyrimidine in MeOH was treated with 6 N HCl at
0 °C. The solution was stirred at room temperature for 2
h and the MeOH was removed *in vacuo*.
6-(Benzofurazan-5-yl)-1,2,3,6-tetrahydro-
5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-
15 phenylpiperidin-1-yl)propyl]}carboxamidopyrimidine
hydrochloride was obtained as a white powder: mp 134-137
°C.

Example 9

20 4-(3-METHOXY)-PHENYL PIPERIDINE: HCl salt; mp 150-154 °C;
¹H NMR δ 2.04 (s, br, 2H), 2.25 (s, br, 2H), 2.80 (s, br,
1H), 3.09 (s, br, 2H), 3.66 (s, 2H), 3.78 (s, 3H), 6.79
(s, br, 3H), 7.23 (s, 1H), 9.41 (s, br, 1H). Anal.
Calcd. For C₁₂H₁₈NOCl + 0.30 CH₂Cl₂: C, 58.34; H, 7.40; N,
25 5.53. Found: C, 58.30; H, 7.71; N, 5.35.

(+)-1,2,3,6-TETRAHYDRO-1-N-[4-(3-METHOXY)-PHENYL]-PIPERID
IN-1-YL]-PROPYL-CARBOXAMIDO-4-METHOXYMETHYL-6-(3,4-
DIFLUOROPHENYL)-2-OXOPYRIMIDINE-5-CARBOXYLIC ACID METHYL
30 ESTER: mp 80-84 °C; [α]_D = +94.7, (c = 0.25, MeOH); ¹H NMR
δ 1.74-1.84 (m, 6H), 1.99-2.09 (m, 2H), 2.38-2.51 (m, 3H),
3.03 (d, J=11.1 Hz, 2H), 3.24-3.43 (m, 2H), 3.48 (s,
3H), 3.71 (s, 3H), 3.80 (s, 3H), 4.72 (s, 2H), 6.68 (s,
1H), 6.72-6.84 (m, 3H), 7.05-7.11 (m, 2H), 7.15-7.27 (m,

-154-

2H), 7.72 (s, 1H), 8.84 (t, J=5.4 Hz, 1H). Anal. Calcd. For $C_{30}H_{33}N_4O_6F_2Cl$: C, 57.8; H, 6.0; N, 9.0. Found: C, 57.61; H, 6.57; N, 6.97.

5 **Example 10**

(+)-1,2,3,6-TETRAHYDRO-1-{N-[4-(3,-ACETAMIDO)-PHENYL-PIPERIDIN-1-YL]PROPYL}CARBOXAMIDO-4-METHOXYMETHYL-6-(3,4-DIFLUORO-PHENYL)-2- OXOPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER: mp 135-138 °C; $[\alpha]_D = +105.5$, (c = 0.11, MeOH);

10 ESMS, 614.25 (M+1); 1H NMR δ 1.76-1.87 (m, 6H), 2.03-2.13 (m, 2H), 2.18 (s, 3H), 2.49 (t, J=6.9 Hz, 3H), 3.10 (d, J=11.1 Hz, 2H), 3.30-3.42 (m, 2H), 3.46 (s, 3H), 3.71 (s, 3H), 4.68 (s, 2H), 6.68 (s, 1H), 6.96 (d, J=7.5 Hz, 1H), 7.04-7.11 (m, 2H), 7.16-7.26 (m, 2H), 7.34 (d, J=6.3 Hz, 1H), 7.45 (s, 1H), 7.94 (s, 1H), 8.97 (t, J=5.4 Hz, 1H);

15 ESMS, M+1 614.25

The compound of Example 10 may also be prepared via hydrogenation of the compound of example 2 (H_2 balloon method, methanol, Pd/C, overnight). A synthetic path

20 analogous to the latter route (Scheme 11) was used in the preparation of the tritiated analog, which in turn, was used as a radioligand in the MCH pharmacological assays.

25 **Example 11**

3-(4-PHENYLPYPERIDIN-1-YL)PROPIONITRILE: Acrylonitrile (3.1 mL, 44 mmol, 2.5 eq) was added to a solution of 4-phenylpiperidine (3.00 g, 18.0 mmol) in EtOH (40 mL) and the mixture was stirred at room temperature for 1.5

30 h. The volatiles were removed, giving 3.80 g of the desired product (brown oil, 99%).

3-(4-PHENYLPYPERIDIN-1-YL)PROPYLAMINE: A solution of BH_3 in THF (1.0 M, 83.0 mL, 83.0 mmol, 3.5 eq) was added to a

-155-

stirring solution of 3-(4-phenylpiperidin-1-yl)-
propionitrile (5.10 g, 24.0 mmol) in anhydrous THF (20
mL) under argon at room temperature. The mixture was
heated at reflux temperature for 4.5 hours and then
5 cooled to room temperature. Aqueous 6 N HCl (130 mL) was
added and stirring was continued for 2 hours at 50-70 °C.
The mixture was basified to pH 9 by addition of aqueous 6
N NaOH and extracted with EtOAc (100 mL) and CH₂Cl₂ (3 x
100 mL). The combined organic extracts were dried over
10 magnesium sulfate and concentrated. The residue was
dissolved in CH₂Cl₂ (20 mL) and treated with HCl in ether
(1.0 M, 50 mL). The solvents were removed, ether (250
mL) was added, the mixture was filtered, and the filter
cake was washed with ether. Water (60 mL) was added to
15 the resulting white solid, 1 N NaOH was added until pH
10-11 was reached, and then the aqueous phase was
extracted with CH₂Cl₂ (3 X 50 mL). The combined extracts
were dried over magnesium sulfate and the solvents were
evaporated, giving the desired product (4.50 g, 87%).

20 6-(3,4-DIFLUOROPHENYL)-1,2,3,6-TETRAHYDRO-5-METHOXYCARBON
YL-4-METHYL-2-OXO-1-{N-[3-(4-PHENYLPYPERIDIN-1-YL)
PROPYL]}CARBOXAMIDO-PYRIMIDINE: A solution of 6-(3,4-
difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxy
25 carbonyl-4-methyl-1-{N-[3-(4-phenyl-piperidin-1-yl)
propyl]}carboxamidopyrimidine (100 mg, 0.185 mmol, mp =
43-45 °C) in MeOH (5 mL) was treated with aqueous 6 N HCl
(1.5 mL) at 0 °C. The solution was stirred at room
temperature for 2 hrs and MeOH was removed *in vacuo*.
30 6-(3,4-Difluorophenyl)-1,2,3,6-tetrahydro-
5-methoxycarbonyl-4-methyl-2-oxo-1-{N-[3-(4-
phenylpiperidin-1-yl)propyl]}carboxamidopyrimidine
hydrochloride was obtained as a white powder (89 mg,
86%). mp 133-136 °C.

35

-156-

Example 12

3-[(3,4,5-TRIFLUOROPHENYL)METHYLENE]-2,4-PENTANEDIONE: A stirring mixture of 3,4,5-trifluorobenzaldehyde (4.2 g, 26.2 mmol), 2,4-pentanedione (2.62 g, 26.2 mmol),
5 piperidine (0.430 g, 5 mmol) in benzene (150 mL) was heated at reflux temperature (equipped with a Dean-Stark trap) for 8 h. The benzene was evaporated, the yellow oily residue, 2-[(3,4,5-trifluorophenyl)-methylene]-2,4-pentanedione, was used in the next step without further
10 purification.

6-(3,4,5-TRIFLUOROPHENYL)-1,6-DIHYDRO-2-METHOXY-5-ACETYL-4-METHYLPYRIMIDINE: A stirring mixture of 2-[(3,4,5-trifluoro-phenyl)methylene]-2,4-pentanedione (26.2 mmol),
15 O-methylisourea hydrogen sulfate (3.22 g, 39.3 mmol), and NaHCO₃ (6.60 g, 78.6 mmol) in EtOH (400 mL) was heated at 95-100 °C for 6 h. The mixture was filtered, the solid residue was washed with ethanol (100 mL). The solvent was evaporated from the combined filtrates and the crude
20 product was purified by flash column chromatography (EtOAc/hexane, 9/1 to 4/1), giving the desired product as an oil (2.80 g, 36%).

6-(3,4,5-TRIFLUOROPHENYL)-1,6-DIHYDRO-2-METHOXY-5-ACETYL-4-METHYL-1-[(4-NITROPHENYLOXY)CARBONYL]PYRIMIDINE:
25 4-Nitrophenyl chloroformate (1.886 g, 9.38 mmol) was added to a solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methylpyrimidine (2.80 g, 9.38 mmol) and pyridine (10 mL) in CH₂Cl₂ (200 mL) at
30 0-5 °C and then the mixture was allowed to warm to room temperature. After 12 h, the solvent was evaporated and the residue was purified by flash chromatography (CH₂Cl₂/EtOAc, 9/1 to 20/3), giving the desired product as a white powder (4.0 g, 92%).

35

-157-

6-(3,4,5-TRIFLUOROPHENYL)-1,2,3,6-TETRAHYDRO-2-OXO-5-ACETYL-4-METHYL-1-[(4-NITROPHENYLOXY)CARBONYL]PYRIMIDINE:
Aqueous 6 N aqueous HCl (4 mL) was added to a stirring solution of 6-(3,4,5-trifluorophenyl)-1,6-dihydro-2-methoxy-5-acetyl-4-methyl-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (4.0 g, 8.63 mmol) in THF (100 mL) at 0-5 °C, and the mixture was allowed to warm to room temperature. After 2 h, the solvent was evaporated and the product was dried under vacuum, giving the desired product as a pure single component which was used in the next step without further purification (3.88 g, 100%).

(+)-1,2,3,6-TETRAHYDRO-1-{N-[4-(4-FLUOROPHENYL)-PIPERIDINE-1-YL]-PROPYL}CARBOXAMIDO-5-ACETYL-2-OXO-6-(3,4,5-TRIFLUOROPHENYL)-4-METHYLPYRIMIDINE HYDROCHLORIDE: ^1H NMR δ 7.20-6.86 (m, 6 H), 6.64 (s, 1 H), 5.56 (s, 1 H), 3.70-3.80 (m, 2 H), 3.43-3.35 (m, 2 H), 3.19-2.98 (m, 2 H), 2.40 (s, 3 H), 2.28 (s, 3 H), 2.50-1.60 (m, 8 H).

Example 13

N1-[4-([4-(DIBUTYLAMINO)BENZYL]AMINOMETHYL)CYCLOHEXYL]-1-NAPHTH-AMIDE: ^1H NMR δ 8.26 (dd, 1 H, $J=2.1, 7.2$ Hz), 7.87 (m, 2 H), 7.51 (m, 2 H), 7.40 (apparent t, 1 H, $J=7.8$ Hz), 7.17 (d, 1 H, $J=8.7$ Hz), 6.61 (d, 2 H, $J=8.7$ Hz), 5.94 (d, 1 H, $J=8.1$ Hz), 4.04 (m, 1 H), 3.76 (m, 1 H), 3.63 (m, 2 H), 3.21 (t, 4 H, $J=7.6$ Hz average), 2.53 (d, 2 H, $J=6.7$ Hz), 2.10, ABm, 4 H), 1.55 (p, 4 H, $J=7.7$ Hz average), 1.34 (sept, 4 H, $J=7.6$ Hz average), 1.17 (m, 4 H), 0.95 (t, 6 H, $J=7.6$ Hz average).

Example 14

(+)-1,2,3,6-TETRAHYDRO-1-{N-[4-(1-NAPHTHYL)-PIPERIDIN-1-YL]PROP-YL}CARBOXAMIDO-4-METHOXYMETHYL-6-(3,4-

-158-

DIFLUOROPHENYL)-2-OXO-PYRIMIDINE-5-CARBOXYLIC ACID METHYL
ESTER: mp 168-172 °C; $[\alpha]_D = +94.7$, ($c = 0.25$, MeOH); ^1H
NMR δ 1.75-1.84 (m, 2H), 1.87-2.01 (m, 4H), 2.14-2.28 (m,
2H), 2.47 (t, $J=7.2$ Hz, 2H), 3.10 (d, $J=11.1$ Hz, 2H),
5 3.28-3.45 (m, 3H), 3.48 (s, 3H), 3.71 (s, 3H), 4.68 (s,
2H), 6.70 (s, 1H), 7.05-7.12 (m, 2H), 7.16-7.24 (m, 1H),
7.42-7.54 (m, 4H), 7.69-7.75 (m, 2H), 7.85 (d, $J=11.4$ Hz,
1H), 8.09 (d, $J=11.1$ Hz, 1H), 8.91 (t, $J=5.4$ Hz, 1H).

10 **Example 15**

4-(5-FLUORO-2-METHOXY) PHENYL PIPERIDINE: mp 254-258 °C; ^1H
NMR δ 1.53-1.68 (m, 2H), 1.79 (d, $J=11.7$ Hz, 2H), 2.12 (dt,
 $J=2.1$ Hz, $J=11.7$ Hz, 1H), 2.77 (dt, $J=1.8$ Hz, $J=12.3$ Hz,
1H), 2.90-3.05 (m, 1H), 3.10-3.22 (m, 2H), 3.68 (s, 1H),
15 3.79 (s, 3H), 6.72-6.93 (m, 3H). Anal. Calcd. For
 $\text{C}_{13}\text{H}_{17}\text{NOFCl} + 0.14 \text{CH}_2\text{Cl}_2$: C, 56.60; H, 6.76; N, 5.44.
Found: C, 56.60; H, 6.92; N, 5.28.

(+)-1,2,3,6-TETRAHYDRO-1-(N-[4-(5-FLUORO-2-METHOXY) PHENYL
20 PIPERIDIN-1-YL] PROPYL) CARBOXAMIDO-4- METHOXYMETHYL-6-
(3,4-DIFLUORO-PHENYL)-2-OXOPYRIMIDINE-5-CARBOXYLIC ACID
METHYL ESTER: ^1H NMR δ 8.93 (t, 1 H, $J=5.4$ Hz), 7.76 (br, 1
H), 7.30-6.69 (m, 7 H), 4.69 (s, 2 H), 3.79 (s, 3 H),
3.71 (s, 3 H), 3.48 (s, 3 H), 3.38 (m, 2 H), 3.10-2.80
25 (m, 3 H), 2.42 (t, 2 H, $J=7.2$ Hz), 2.07 (dt, 2 H, $J=3.0$,
8.4 Hz), 2.00-1.60 (m, 6 H).

Example 16

(+)-1,2,3,6-TETRAHYDRO-1-(N-[4-HYDROXY-4-(2-PYRIDYL)-PIPE
30 RIDIN-1-YL] PROPYL) CARBOXAMIDO-4- METHOXYMETHYL-6-
(3,4-DIFLUOROPHENYL)-2- OXOPYRIMIDINE-5-CARBOXYLIC ACID
METHYL ESTER: mp 132-135 °C; $[\alpha]_D = +94.7$, ($c = 0.25$,
MeOH); ^1H NMR δ 1.47 (d, $J=11.7$ Hz, 2H), 1.74-1.85 (m, 2H),
2.43-2.63 (m, 9H), 2.87 (d, $J=10.2$ Hz, 2H), 3.30-3.47 (m,

-159-

2H), 3.49 (s, 3H), 3.71 (s, 3H), 4.69 (s, 2H), 6.69 (s, 1H), 7.04-7.21 (m, 4H), 7.49 (dd, J=0.6 Hz, J=6.9 Hz, 1H), 7.72 (s, br, 1H), 8.36 (dd, J=1.2, 4.8 Hz, 1H), 8.89 (t, J=5.4 Hz, 1H).

5

Example 17**1-(3-AMINOPROPYL)-4-[2-PYRIDYL]PYRIDINIUM BROMIDE**

HYDROBROMIDE: A solution of 2,4'-dipyridyl (25.0 g, 160 mmol) and 3-bromopropyl-amine hydrobromide (35.0 g, 160 mmol) in DMF (60 mL) was heated at 90-95 °C for 10 h. After cooling to room temperature, anhydrous ether (500 mL) was added to the mixture, the resulting white solid was filtered, washed with Et₂O and dried, giving 1-(3-aminopropyl)-4-[2-pyridyl]pyridinium bromide hydrobromide (60 g, 100%). ¹H NMR (DMSO-d₆) δ 2.35-2.44 (m, 2 H), 3.08-3.13 (m, 2 H), 4.76-4.81 (m, 2 H), 7.58 (dd, J=4.8 Hz, J=7.5 Hz, 1 H), 8.03 (dt, J=1.8 Hz, J=7.8 Hz, 1 H), 8.32 (d, J=7.8 Hz, 1 H), 8.77-8.81 (m, 3 H), 9.12 (d, J=6.3 Hz, 2 H). Anal. Calcd. for C₁₃H₁₆N₃Br + HBr + 0.5 H₂O: C, 40.65; H, 4.72; N, 10.94. Found: C, 40.83; H, 4.37; N, 11.05.

3-(3',6'-DIHYDRO-2'-H-[2,4']BIPYRIDINYL-1'-YL)-PROPYLAMINE: NaBH₄ (2 g, 53 mmol) in small portions was added to a solution of 1-(3-aminopropyl)-4-[2-pyridyl]pyridinium bromide hydrobromide (6 g, 16 mmol) in MeOH (150 mL) at 0-5 °C over a period of 2 h. The reaction mixture was stirred overnight at room temperature and then the solvent was evaporated. The residue was suspended in ether (200 mL) and treated with aqueous 50% NaOH solution (100 mL). The ether layer was separated and the aqueous layer was extracted with additional ether (2 X 50 mL). The combined ether extracts were dried over potassium carbonate and the solvent was removed, giving

-160-

3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine (3.48 g) as an oil. The crude product was used in the next step immediately without further purification.

5

3-AMINOPROPYL-4-(2-PYRIDYL)PIPERIDINE: A suspension of 3-(3',6'-dihydro-2'-H-[2,4']bipyridinyl-1'-yl)-propylamine (3.48 g crude, 15.9 mmol) and Pearlman's catalyst (1.0 g) in MeOH (40 mL) was hydrogenated under 120 psi for 10 h, after which the reaction mixture was filtered through a pad of Celite and the solvent was removed. The residue was purified by column chromatography over silica gel (30 g) [Note: If a large excess of silica gel is used the recovery of the product will be very low] (CH₂Cl₂/methanol/2M NH₃ in MeOH, 90/8/4 to 90/40/40). The product was obtained as a pale yellow oil (3.21 g, 91%).
¹H NMR δ (CD₃OD) 1.50-1.99 (m, 10 H), 2.02-2.06 (m, 2 H), 2.37-2.75 (m, 3 H), 3.02-3.06 (br m, 2 H), 7.05-7.09 (m, 4 H), 7.16 (dt, J=0.9 Hz, J=8.7 Hz, 1 H), 8.48 (dd, J=0.9 Hz, J=4.2 Hz, 1 H).

20

Part II

(+)-6-(3,4-DIFLUOROPHENYL)-1-{N-[4-(2-PYRIDYL)PIPERIDIN-1-YL]-PROPYL} CARBOXAMIDO-5-METHOXYCARBONYL-4-METHOXYMETHYL-2-OXO-1,2,3,6-TETRAHYDROPYRIMIDINE DIHYDROCHLORIDE

25

5-METHOXYCARBONYL-4-METHOXYMETHYL-1,2,3,6-TETRAHYDRO-2-OXO-6-(3,4-DIFLUOROPHENYL)-PYRIMIDINE: Copper(I) oxide (5.06 g, 0.035 mole) and acetic acid (2.05 mL) were added sequentially to a stirring solution of methyl 4-methoxyacetoacetate (50.0 g, 0.351 mol), 3,4-difluorobenzaldehyde (51.4 g, 0.351 mmol), and urea (31.6 g, 0.527 mole) in THF (300 mL) at room temperature, followed by dropwise addition of boron trifluoride

30

35

-161-

diethyl etherate (56.0 mL, 0.456 mole). The mixture was stirred at reflux temperature for 8 h, whereupon TLC (1/1 EtOAc/hexanes) indicated completion of the reaction. The reaction mixture was cooled and poured into a mixture of ice and sodium bicarbonate (100 g) and the resulting mixture was filtered through Celite. The Celite pad was washed with dichloromethane (400 mL). The organic layer was separated from the filtrate and the aqueous layer was extracted with more dichloromethane (3 X 300 mL). The combined organic extracts were dried (sodium sulfate) and the solvent was evaporated. The crude product was purified by flash chromatography (ethyl acetate/hexanes, 1/1; then ethyl acetate), giving the desired product as a pale yellow foam. The foam was triturated with hexanes, giving a white powder (103.3 g, 94%). ^1H NMR δ 3.476 (s, 3H), 3.651 (s, 3H), 4.653 (s, 2H), 5.39 (s, 1H), 6.60 (br s, 1H, NH), 7.00-7.20 (m, 3H), 7.72 (br s, 1H, NH).

(+)-5-METHOXYCARBONYL-4-METHOXYMETHYL-1,2,3,6-TETRAHYDRO-2-OXO-6-(3,4-DIFLUOROPHENYL)-PYRIMIDINE: The racemic intermediate 5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)pyrimidine was resolved by chiral HPLC [Chiralcel OD 20 X 250 mm #369-703-30604; λ 254 nm; hexanes/ethanol 90/10; 85 mg per injection; retention time of the desired enantiomer: 16.94 min., the first enantiomer peak to elute], giving (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-pyrimidine (40-42 wt% isolation of the desired enantiomer from the racemate); $[\alpha]_D = +83.8$ (c = 0.5, chloroform).

(+)-5-METHOXYCARBONYL-4-METHOXYMETHYL-1,2,3,6-TETRAHYDRO-2-OXO-6-(3,4-DIFLUOROPHENYL)-1-[(4-NITROPHENYLOXY) CARBONYL

-162-

L]PYRIMIDINE: A solution of lithium hexamethyldisilazide in THF (1M, 18.0 mL, 18.0 mmol) was added over 2-3 min. to a solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-pyrimidine (1.98 g, 6.34 mmol) in anhydrous THF (20 mL) at -78 °C under argon atmosphere and the mixture was stirred for 10 min. The resulting solution was added over 6 min., via a cannula, to a stirred solution of 4-nitrophenyl chloroformate (4.47 g, 22.2 mmol) in THF (20 mL) at -78 °C. The mixture was stirred for an additional 10 min. and the mixture was poured onto ice (50 g) and extracted with chloroform (2 X 50 mL). The combined extracts were dried (sodium sulfate) and the solvent evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate, 4/1 to 3.5/1), giving the product as a yellow syrup, which on trituration with hexanes became a white powder (2.40 g, 79%). ¹H NMR δ 3.52 (s, 3H), 3.74 (s, 3H), 4.65-4.80 (q, J=16.5 Hz, 2H), 6.32 (s, 1H), 7.10-7.30 (m, 4H), 7.36 (d, J=9 Hz, 2H), 8.27 (d, J=9 Hz, 2H).

20

(+)-6-(3,4-DIFLUOROPHENYL)-1-(N-[4-(2-PYRIDYL)PIPERIDIN-1-YL]-PROPYL)CARBOXAMIDO-5-METHOXYCARBONYL-4-METHOXYMETHYL-2-OXO-1,2,3,6-TETRAHYDROPYRIMIDINE

DIHYDROCHLORIDE: A solution of (+)-5-methoxycarbonyl-4-methoxymethyl-1,2,3,6-tetrahydro-2-oxo-6-(3,4-difluorophenyl)-1-[(4-nitrophenyloxy)carbonyl]pyrimidine (2.38 g, 5 mmol), 3-aminopropyl-4-(2-pyridyl)piperidine (1.21 g, 5.5 mmol) in THF (20 mL) was stirred at room temperature for 12 h. The solvent was evaporated and the residue was re-dissolved in ethyl acetate (100 mL). The resulting solution was washed with ice-cold 1 N NaOH (4 X 50 mL), brine (2 X 50 mL) and dried over potassium carbonate. The solvent was evaporated in vacuo and the residue was purified by flash chromatography (dichloromethane/MeOH/2 M ammonia in MeOH, 980/10/10 to 940/30/30), giving a

-163-

clean fraction of the desired product (2.45 g, 88%) as a foam and a slightly impure fraction (0.30 g, 10%). ¹H NMR δ 1.60-2.00 (m, 6H), 2.05-2.15 (m, 2H), 2.38-2.43 (br t, 2H), 2.65-2.80 (m, 1H), 3.05-3.06 (br d, 2H), 3.30-3.45 (m, 2H), 3.48 (s, 3H), 3.704 (s, 3H), 4.68 (s, 2H), 6.68 (s, 1H), 7.05-7.20 (m, 5H), 7.58-7.63 (dt, 1H), 7.70 (s, 1H, NH), 8.50-8.52 (dd, 1H), 8.88 (br t, 1H).

The HCl salt was prepared by treatment of a solution of the free base in ether with 1 N HCl in ether. The white powder was dried under reduced pressure: ¹H NMR δ 2.05-2.20 (m, 4H), 2.77-2.88 (m, 2H), 3.00-3.20 (m, 4H), 3.35-3.47 (m, 2H), 3.47 (s, 3H), 3.64-3.70 (m, 2H), 3.71 (s, 3H), 4.05 (br t, 1H), 4.67 (s, 2H), 6.59 (s, 1H), 7.05-7.20 (m, 3H), 7.79 (t, 1H), 8.00 (d, 1H), 8.43 (dt, 1H), 8.96 (br t, 1H, NH), 12.4 (br s, 1H). m.p. 188-191 °C; [α]_D = +141.13 (c = 0.265, MeOH); Anal. Calcd. for C₂₈H₃₄N₅O₅F₂Cl + 0.6 H₂O: C, 52.36; H, 5.84; N, 10.90. Found: C, 52.24; H, 5.96; N, 10.80. (Note: NMR analysis of this product did not show the presence of any water. However, it was noted by the lab that performed the elemental analysis that this sample gains weight during handling by absorbing water from the atmosphere).

Example 18

(1)-1,2,3,6-TETRAHYDRO-1-{N-[4-(ISOBENZOFURAN) PIPERIDINE-1-YL]-PROPYL}CARBOXAMIDO-5-METHOXYCARBONYL-2-OXO-6-(3,4-BENZOFURAZAN)-4-METHYLPYRIMIDINE HYDROCHLORIDE

4-(3,4-BENZOFURAZAN)-6-METHYL-2-OXO-3-{[3-(4-SPIRO[ISOBENZOFURAN-1(3H),4'-PIPERIDINE]PROPYL)-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER : 1-(3-Aminopropyl)-4- spiro[iso-benzofuran-1 (3H),4'-

-164-

piperidine] (0.028 g, 0.110 mmol) was added to
(±)-6-(benzofurazan)-1,6-dihydro-2-methoxy-
5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyri
midine (0.047 g, 0.100 mmol) in dry dichloromethane (10
5 mL) and the solution was stirred at room temperature for
24 h. Aqueous 6 N HCl (2 mL) was added to the reaction
mixture which was stirred for another 1 h. The reaction
mixture was basified with aqueous 10% KOH solution (pH =
9) and extracted into dichloromethane (3 x 10 mL). The
10 organic layer was dried over sodium sulfate, filtered and
concentrated. The crude product was purified by flash
chromatography (EtOAc/ MeOH, 4.5/0.5), giving the desired
product (41.0 mg, 73 %) as a syrup: $^1\text{H NMR}$ δ 1.76-1.81
(m, 7 H), 1.94-2.04 (m, 6 H), 2.32-2.48 (m, 1 H), 2.83
15 (d, J=10.6 Hz, 2 H), 3.36-3.43 (m, 2 H), 3.75 (s, 3 H),
5.05 (s, 2 H), 6.83 (s, 1 H), 7.07-7.27 (m, 4 H), 7.54
(d, J=9.5 Hz, 1 H), 7.69 (s, 1 H), 7.78 (d, J=9.5 Hz, 1
H), 8.85 (d, J=5.2 Hz, 1 H).

20 HCl in ether (1 N, 5 mL) was added to the free base
(0.041 g, 0.073 mmol) in dichloromethane (4 mL), and the
solution was concentrated under reduced pressure. The
product was recrystallized from ether, giving the
hydrochloride salt as a pale yellow solid (42.0 mg, 96
25 %); mp 180-182 °C; Anal. Calcd. for $\text{C}_{29}\text{H}_{34}\text{N}_6\text{O}_6\text{Cl}$ + 0.5 moles
 H_2O : C, 57.47; H, 5.65; N, 13.87. Found: C, 57.42; H,
5.71; N, 13.70.

Example 19

30 2-(3,4-DIFLUOROPHENYL)4,5-DIHYDROIMIDAZOLE-1-CARBOXYLIC
ACID {3-[4-PHENYL-4-(4-BROMO-5-METHYLTHIOPHEN-2-YL)]
-PROPYL}-AMIDE: Anal. Calcd. for $\text{C}_{30}\text{H}_{30}\text{N}_4\text{O}_5\text{ClF}_3$ + HCl + 1.5
 H_2O : C, 55.26; H, 6.03; N, 8.59. Found: C, 55.29; H, 5.95;
N, 8.39.

35

-165-

Example 20

4-(3,4-DIFLUOROPHENYL)-6-METHYL-2-OXO-3-{{3-(4-SPIRO[ISOBENZOFURAN-1(3H),4'-PIPERIDINE]PROPYL)-1,2,3,4-TETRAHYDOPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER

5 For the preparation of the ether piperidine precursor of the compound of Example 20, refer to W.E.Parham et al, *J. Org. Chem.* (1976) 41, 2268.

10 1-TERT-BUTOXYCARBONYL-3-(4-SPIRO[ISOBENZOFURAN-1(3H),4'-PIPERIDINE])PROPYLAMINE: N-(tert-butoxycarbonyl)-3-bromopropylamine (0.772 g, 3.27 mmol) and potassium carbonate (0.904 g, 6.54 mmol) were added to a stirring solution of the amine (0.566 g, 3.27 mmol) in dioxane (20 mL) and the reaction mixture was heated at reflux temperature for
15 24 h. The reaction mixture was cooled to room temperature, concentrated and partitioned between chloroform (40 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography
20 (ethyl acetate/ methanol, 4.5/0.5), giving the desired product (0.856 g, 79 %) as a colorless oil; ¹H NMR δ 1.45 (s, 9 H), 1.63-2.04 (m, 6 H), 2.33-2.52 (m, 4 H), 2.87 (d, J=11.0 Hz, 2 H), 3.2 (br s, 2 H), 5.07 (s, 2 H), 5.6 (br s, 1 H), 7.13-7.28 (m, 4 H).

25

3-(4-SPIRO[ISOBENZOFURAN-1(3H),4'-PIPERIDINE])PROPYLAMINE: Trifluoroacetic acid (1 mL) was added to 1-tert-butoxycarbonyl 3-(4-spiro[isobenzofuran-1(3H),4'-piperidine])propylamine (0.500 g, 1.51 mmol) in
30 dichloromethane (5 mL) and the solution was stirred at room temperature for 1 h. The reaction mixture was concentrated, neutralized with 10 % KOH solution and extracted into dichloromethane (25 mL). The organic layer was dried over sodium sulfate, filtered and

-166-

concentrated, giving the desired amine (0.340 g, 98%) which was used in the subsequent step without further purification.

5 4-(3,4-DIFLUOROPHENYL)-6-METHYL-2-OXO-3-([3-(4-SPIRO[ISOBENZOFURAN-1(3H),4'-PIPERIDINE]PROPYL)-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER: 3-(4-spiro[isobenzofuran-1(3H),4'-piperidine]) propylamine (0.0319 g, 0.123 mmol) was added to
10 (\pm)-6-(3,4-Difluorophenyl)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (0.052 g, 0.112 mmol) in dry dichloromethane (10 mL) and the solution was stirred at room temperature for 24 h. Aqueous 6 N HCl (2 mL) was added and the reaction
15 mixture was stirred for an additional 1 h. After neutralization with 10% aqueous KOH solution, the reaction mixture was extracted with dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was
20 purified by flash chromatography (EtOAc/ MeOH, 4.5/0.5), giving the desired product (0.040 g, 64 %) as a syrup; $^1\text{H-NMR}$ δ 1.73-1.78 (m, 7 H), 1.93-2.04 (m, 2 H), 2.33-2.48 (m, 6 H), 2.83 (d, $J=11.8$ Hz, 2 H), 3.35-3.41 (m, 2 H), 3.71 (s, 3 H), 5.06 (s, 2 H), 6.75 (s, 1 H), 7.04-7.26
25 (m, 7 H), 8.82 (t, $J=5.1$ Hz, 1 H).

A solution of 1 N HCl in ether (5 mL) was added to the free base (0.040 g, 0.072 mmol) in dichloromethane (4 mL) and the solution was concentrated in vacuo. The product
30 was recrystallized from ether, giving the dihydrochloride as a pale yellow solid (0.042 g, 99 %); mp 178-182 °C; Anal. Calcd. for $\text{C}_{29}\text{H}_{34}\text{F}_2\text{N}_4\text{O}_5\text{Cl}_2 + 0.6 \text{ H}_2\text{O}$: C, 57.87; H, 5.73, N 9.31. Found: C, 58.11; H 5.90; N 8.95.

-167-

Example 21

1,2,3,6-TETRAHYDRO-1-{N-[4-(DIHYDROINDENE)-1-YL}PROPYL}CARBOXYAMIDO-5-METHOXYCARBONYL- 2-OXO-6-(3,4-BENZOFURAZAN)-4-METHYLPYRIMID-INE

5

For the preparation of the indane piperidine precursor of the compound of Example 21, refer to M.S.Chambers *J. Med. Chem.* (1992) 35,2033.

10 N-(tert-butoxycarbonyl)-3-(4-spiro[isobenzofuran-1(3H),4'-piperidine])propylamine (1.10 g, 4.64 mmol) and potassium carbonate (1.17 g, 8.44 mmol) were added to a stirring solution of the amine (0.790 g, 4.22 mmol) in dioxane (20 ml), and the resulting solution was heated at
15 reflux temperature for 24 h. The reaction mixture was cooled to room temperature, concentrated and partitioned between chloroform (40 mL) and water (5 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column
20 chromatography (ethyl acetate/ methanol, 4.5/0.5), giving the desired product (0.886 g, 61 %) as a colorless oil; ¹H NMR δ 1.46 (s, 9 H), 1.55 (d, J = 11.3 Hz, 2 H), 1.69 (t, J = 6.3 Hz, 2 H), 1.88-2.47 (m, 6 H), 2.47 (t, J = 6.3 Hz, 2 H), 2.88 (t, J = 3.3 Hz, 4 H), 3.23 (d, J = 5.6 Hz,
25 2 H), 5.85 (br s, 1 H), 7.18 (s, 4 H).

Trifluoroacetic acid (1 ml) was added to 1-tert-butoxycarbonyl-3-(4-spiro[isobenzofuran-1(3H),4'-piperidine])propylamine (0.180 g, 0.52 mmol) in
30 dichloromethane (5 ml) and the resulting solution was stirred at room temperature for 1 hour. The solution was concentrated, neutralized with 10% KOH solution and extracted into dichloromethane (25 ml). The organic layer was dried over sodium sulfate, filtered and

-168-

concentrated, giving propylamine (0.156 g, 100%) which was used in the subsequent step without further purification.

5 (±)-4-(3,4-BENZOFURAZAN)-6-METHYL-2-OXO-3-{SPIRO[1H-INDAN
E-1,4'-PIPERIDINE]PROPYL}-1,2,3,4-TETRAHYDROPYRIMIDINE-5-
CARBOXYLIC ACID METHYL ESTER HYDROCHLORIDE: To
 (±)-4-(3,4-benzofurazan)-1,6- dihydro-2-methoxy-5-
10 methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)-
 carbonylpyrimidine (0.059 g, 0.126 mmol) in dry
 dichloromethane (10 mL), 1-(3-aminopropyl)spiro
 [1H-indane-1,4'- piperidine] (0.062 g, 0.252 mmol) was
 added and the solution was stirred at room temperature
15 for 24 h. The reaction mixture was stirred for another 1
 h after addition of 2 mL of 6N HCl. The reaction mixture
 was basified with 10% aqueous KOH solution (pH = 9) and
 extracted with dichloromethane (3 x 10 mL). The combined
 organic extracts were dried over sodium sulfate, filtered
20 and concentrated. The crude product was purified by
 flash chromatography (EtOAc/ MeOH, 4.5/0.5), giving 0.070
 g (100%) of the desired product as a syrup: ¹H NMR δ 1.51
 (d, J=12.5 Hz, 2 H), 1.76-2.08 (m, 4 H), 2.12 (t, J=10.3
 Hz, 2 H), 2.45 (s, 5 H), 2.86-2.91 (m, 4 H), 3.30-3.45
 (m, 2 H), 3.75 (s, 3 H), 6.83 (s, 1 H), 7.02 (br s, 1 H),
25 7.0 (m, 4 H), 7.54 (d, J=9.6 Hz, 1 H), 7.69 (s, 1 H),
 7.78 (d, J=9.2 Hz, 1 H), 8.84, (t, J=5.2 Hz, 1 H).

 To the free base (0.070 g, 0.125 mmol) in 4 mL of
 dichloromethane, 5 mL of 1 N HCl in ether was added, and
30 the solution was concentrated under reduced pressure.
 Recrystallization from ether gave 0.088 g (100 %) of
 (±)-4-(3,4-benzofurazan)-6-methyl-2-oxo-3-{spiro[1H-indan
e- 1,4'-piperidine]propyl}-1,2,3,4-tetrahydro-
 pyrimidine-5-carboxylic acid methyl ester hydrochloride
35 as a white solid: m.p. 155-157 °C; Anal. Calcd. for

-169-

$C_{30}H_{36}N_6O_5Cl$: C, 57.12; H, 5.76; N, 13.33. Found: C, 57.40; H, 5.96; N, 13.02.

Example 22

5 (+)-1,2,3,6-TETRAHYDRO-1-{N-[4-(BENZO-4',5' (H) FURAN) PIPERIDIN-1- YL] PROPYL} CARBOXAMIDO-4-ETHYL- 6-(3,4-DIFLUOROPHENYL)-2-OXO- PYRIMIDINE-5-CARBOXAMIDE HYDROCHLORIDE: DMAP · ECD (0.250 mmol, 0.050 g) was added to a stirred mixture of (+)-1,2,3,6-tetra-hydro-1-
10 {N-[4-(benzo-4',5' (h) furan) piperidin-1-yl] propyl} carbox-amido-4-ethyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine-5-carboxyl-ic acid hydrochloride (0.100 mmol, 0.055 g) and N-methylmorpholine (0.330 mL) in dry dichloromethane (10 mL). The resulting mixture was stirred at room
15 temperature for 1 h and quenched with NH_3 . The reaction mixture was stirred at room temperature overnight, concentrated and chromatographed, giving the desired product. The HCl salt was prepared by the addition of HCl in ether to a solution of the product in
20 dichloromethane, followed by evaporation of the solvents. Anal. Calc. For $C_{29}H_{33}N_5O_4 \cdot F_2 + HCl + 0.7 CHCl_3$: C, 52.96; H, 5.29; N, 9.40. Found: C, 52.81; H, 5.69; N, 8.97.

Example 23

25 (1)-1,2,3,6-TETRAHYDRO-1-{N-[4-(3,4-DIHYDRO-2-OXOSPIRO-NAPHTHALENE-1(2H))-PIPERIDINE-1-YL] PROPYL} CARBOXAMIDO-5-METHOXYCARBONYL-2- OXO-6-(3,4-BENZOFURAZAN)-4-METHYLPYRIMIDINE HYDROCHLORIDE
30 1-(3-TERT-BUTOXYCARBONYLAMINOPROPYL) SPIRO[ISOCROMAN-3,4' PIPERIDIN]-1-ONE: To a stirred solution of spiro [piperidine-4,1'-tetralin] To a stirred solution of spiro[isochroman-3,4'-piperidin]-1-one (K.Hashigaki et al. *Chem.Pharm.Bull.* (1984) 32, 3568.) (0.587 g, 2.58
35 mmol) in dioxane (20 mL), N-(tert- butoxycarbonyl)-

-170-

3-bromopropylamine (0.615 g, 2.84 mmol) and potassium carbonate (0.714 g, 5.17 mmol) were added and the solution was refluxed for 24 h. The reaction mixture was cooled to room temperature, concentrated and partitioned between 40 mL chloroform and 5 mL water. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by column chromatography (ethyl acetate/ methanol, 4.5/0.5) to yield 0.465 g (47 %) of the desired product as a colorless oil; ¹H NMR δ 1.45 (s, 9 H), 1.64-2.18 (m, 7 H), 2.45-2.84 (m, 6 H), 3.19-3.95 (m, 4 H), 6.01 (br s, 1 H), 7.13-7.26 (m, 3 H), 7.42 (d, J=7.7 H).

Step B.

1-(3-AMINOPROPYL) SPIRO[ISOCHROMAN-3,4'PIPERIDIN]-1-ONE:
To 1-(3-tert-Butoxycarbonylaminopropyl)spiro [isochroman-3,4'-piperidin]-1-one (0.144 g, 0.375 mmol) in 5 mL of dichloromethane, 1 mL of trifluoroacetic acid was added and the solution stirred at room temperature for 1 h. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 mL of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated, giving 0.110 g (100%) of the product which was used as such for the subsequent step.

(±)-4-(3,4-BENZOFURAZAN)-6-METHYL-2-OXO-3-((SPIRO[ISOCHROMAN-3,4'-PIPERIDIN]-1-ONE)PROPYL)-1,2,3,4-TETRAHYDOPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER:
To (±)-4-(3,4-Benzofurazan)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)-carbonylpyrimidine (40.0 mg, 0.0865 mmol) in 10 mL of dry dichloromethane, spiro[isochroman-3,4'piperidin]-1-one (44.0 mg, 0.173 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction

-171-

mixture was stirred for another 1 h after addition of 2 mL of 6N HCl. The reaction mixture was basified with 10% aqueous KOH solution (pH = 9) and extracted into dichloromethane (3 x 10 mL). The organic layer was dried
5 over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/ MeOH, 4.5/0.5), giving 50.0 mg (100%) of the desired product as a syrup: $^1\text{H NMR}$ δ 1.67-2.13 (m, 8 H), 2.45 (m, 5 H), 2.70 (t, J=7.4 Hz, 2 H), 2.72-2.75 (m, 2
10 H), 3.19 (t, J=7.4 Hz, 2 H), 3.34-3.45 (m, 2 H), 3.75 (s, 3 H), 6.82 (s, 1 H), 6.87 (s, 1 H), 7.13-7.44 (m, 3 H), 7.54 (d, J=9.6 Hz, 1 H), 7.43 (d, J=7.4 Hz, 1 H), 7.69 (s, 1 H), 7.79 (d, J=9.6 Hz, 1 H), 8.87 (t, J=5.2 Hz, 1 H).

15

To the free base (50.0 mg, 0.084 mmol) in 4 mL of dichloromethane, 5 mL of 1 N HCl in ether was added, and the solution concentrated under reduced pressure. Recrystallization from ether gave 30.0 mg (86 %) of the
20 product as a white solid: m.p. 165-167 °C; Anal. Calcd. for $\text{C}_{31}\text{H}_{36}\text{N}_6\text{O}_6\text{Cl} + 1.5 \text{ H}_2\text{O}$: C, 57.81; H, 5.95. Found: C, 57.75; H, 5.91.

25

Example 24

(1)-1,2,3,6-TETRAHYDRO-1-(N-[4-(3,4-DIHYDRO-2-OXOSPIRO-NAPHTHALENE-1(2H))-PIPERIDINE-1-YL]PROPYL)CARBOXAMIDO-5-M
ETHOXY-CARBONYL-2- OXO-6-(3,4-DIFLUOROPHENYL)-4-METHYL-
PYRIMIDINE

30

(\pm)-4-(3,4-DIFLUOROPHENYL)-6-METHYL-2-OXO-3-{(SPIRO[ISOCROMAN- 3,4'PIPERIDIN]-1-ONE)PROPYL}-1,2,3,4-TETRAHYDRO-PYRIMIDINE-5- CARBOXYLIC ACID METHYL ESTER: To

(\pm)-4-(3,4-Difluorophenyl)- 1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophen-oxy)carbonyl-
35

-172-

pyrimidine (40.0 mg, 0.0865 mmol) in 10 mL of dry dichloromethane, spiro[isochroman-3,4'-piperidin]-1-one (44.0 mg, 0.173 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction mixture was stirred for another 1 h after addition of 2 mL of 6N HCl. The reaction mixture was basified with 10% aqueous KOH solution (pH = 9) and extracted into dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/ MeOH, 4.5/0.5), giving 45.0 mg (90%) of (\pm)-4-(3,4-difluorophenyl)-6-methyl-2-oxo-3-((spiro[isochroman-3,4'-piperidin]-1-one)propyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid methyl ester as a syrup;

^1H NMR δ 1.75-1.94 (m, 9H), 2.05-2.13 (m, 4 H), 2.36-2.41 (m, 5 H), 2.70 (t, J=7.35 Hz, 2 H), 2.77 (m, 2 H), 3.19 (t, J=7.4 Hz, 2 H), 3.39-3.43 (m, 2 H), 6.69 (s, 1 H), 7.04-7.45 (m, 8 H), 8.82 (t, J=5.2 Hz, 1 H).

To the free base (45.0 g, 0.077 mmol) in 4 mL of dichloromethane, 5 mL of 1 N HCl in ether was added, and the solution was concentrated in vacuo. Recrystallization from ether gave 0.050 g (100%) of (\pm)-4-(3,4-difluorophenyl)-6-methyl-2-oxo-3-((spiro[isochroman-3,4'-piperidin]-1-one)propyl)-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester hydrochloride as a white solid: m.p. 150-152 °C; Anal. Calcd. for $\text{C}_{31}\text{H}_{38}\text{F}_2\text{N}_4\text{OCl} + 2 \text{H}_2\text{O}$: C, 56.49; H, 5.96. Found: C, 56.40; H, 5.95.

Example 25

5-[(Z)-1-(1-ETHYL-2,2,4-TRIMETHYL-1,2-DIHYDRO-6-QUINOLINY L)-METHYLIDENE]-2-THIOXO-1,3-THIAZOLAN-4-ONE

-173-

Example 26

1-[BIS(4-FLUOROPHENYL)METHYL]-4-(3-PHENYL-2-PROPENYL)PIPERAZINE

5 **Example 27**

4-[(4-IMIDAZO[1,2-A]PYRIDIN-2-YLPHENYL)IMINO]METHYL-5-METHYL-1,3-BENZENEDIOL

Example 28

10 1-[3-(4-CHLOROBENZOYL)PROPYL]-4-BENZAMIDOPIPERIDINE

Preparation of

1-[3-(4-chlorobenzoyl)propyl]-4-benzamidopiperidine

15 1-[3-(4-CHLOROBENZOYL)PROPYL]-4-BENZAMIDOPIPERIDINE: A mixture of 3-(4-chlorobenzoyl)propyl bromide (640 mg, 2.45 mmol), 4-benzamidopiperidine (500 mg, 2.45 mmol) and K_2CO_3 (1.01 g, 7.34 mmol) in 50 ml of acetone was heated at reflux temperature for 48 h. The cooled reaction mixture
20 was filtered to remove the solids, concentrated in vacuo, giving a yellow solid, which was purified by chromatography (MeOH/ $CHCl_3$, 5/95). The product (320 mg, 33.9%) was isolated as a white powder: 1H NMR δ 1.46 (dq, $J_1=1.0$ Hz, $J_2=8.4$ Hz, 2H), 1.90-2.10 (m, 4H), 2.16 (m, 2H), 2.43 (t, $J=6.9$ Hz, 2H), 2.80-2.90 (m, 2H), 2.97 (t, $J=6.9$ Hz, 2H), 3.97 (m, 1H), 5.92 (d, $J=7.8$ Hz, 1H, N-H),
25 7.40-8.00 (m, 9H). The product was converted to the HCl salt and recrystallized from MeOH/ Et_2O , m.p. 243-244 °C; Anal. Calcd for $C_{22}H_{25}ClN_2O_2 + HCl + H_2O$: C, 60.15; H, 6.37; N, 6.37; Found: C, 60.18; H, 6.34; N, 6.29.

Example 29

4-[4-(4-CHLOROPHENYL)-4-HYDROXY-1-PIPERIDINYL]-1-(4-CHLOROPHENYL)-1-BUTANONE

-174-

Example 30

N-METHYL-8-[4-(4-FLUOROPHENYL)-4-OXOBUTYL]-1-PHENYL-1,3,8-
-TRI-AZASPIRO-[4.5]DECAN-4-ONE

5 **Example 31**

1H-1,2,3-BENZOTRIAZOL-1-YL (2-NITROPHENYL) SULFONE

Example 32

(1)-1,2,3,6-TETRAHYDRO-1-{N-[4-(DIHYDROINDENE)-1-YL]PROPYL}-
10 L)-
CARBOXAMIDO-5-METHOXYCARBONYL-2-OXO-6-(3,4-DIFLUORO)-4-ME-
THYL-PYRIMIDINE

1-(3-TERT-BUTOXYCARBONYLAMINOPROPYL)SPIRO[1H-INDANE-1,4'-
15 PIPERIDINE]: To a stirred solution of spiro[1H-indane-
1,4'-piperidine] (M.S.Chambers et al. *J. Med. Chem.*
(1992) 35, 2033.) (0.790 g, 4.22 mmol) in dioxane (20
mL), N-(tert-butoxy-carbonyl)-3-bromopropylamine (1.1 g,
4.64 mmol) and potassium carbonate (1.17 g, 8.44 mmol)
20 were added and the resulting solution was heated at
reflux temperature for 24 h. The reaction mixture was
cooled to room temperature, concentrated and partitioned
between 40 mL of chloroform and 5 mL of water. The
organic layer was dried over sodium sulfate, filtered and
25 concentrated. The crude product was purified by column
chromatography (ethyl acetate/ methanol, 4.5/0.5) to
yield 0.886 g (61 %) of the required product as a
colorless oil: ¹H NMR δ 1.46 (s, 9 H), 1.55 (d, J=11.3 Hz,
2 H), 1.69 (t, J=6.3 Hz, 2 H), 1.88-2.47 (m, 6 H), 2.47
30 (t, J=6.3 Hz, 2 H), 2.88 (t, J=3.3 Hz, 4 H), 3.23 (d,
J=5.6 Hz, 2 H), 5.85 (br s, 1 H), 7.18 (s, 4 H).

1-(3-AMINOPROPYL)SPIRO[1H-INDANE-1,4'-PIPERIDINE]: To
1-(3-tert- Butoxycarbonylaminopropyl)spiro[1H-indane-

-175-

- 1,4'-piperidine] (0.180 g, 0.52 mmol) in 5 mL of dichloromethane, 1 mL of trifluoroacetic acid was added and the solution stirred at room temperature for 1 h. The solution was concentrated, neutralized with 10 % KOH solution and extracted into 25 mL of dichloromethane. The organic layer was dried over sodium sulfate, filtered and concentrated, giving 0.156 g (100%) of the product which was used as such for the subsequent step.
- (±)-4-(3,4-DIFLUORO)-6-METHYL-2-OXO-3-{SPIRO[1H-INDANE-1, 4'-PIPERIDINE]PROPYL}-1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER: To (±)-4-(3,4-difluoro)-1,6-dihydro-2-methoxy-5-methoxycarbonyl-4-methyl-1-(4-nitrophenoxy)carbonylpyrimidine (50.0 g, 0.108 mmol) in 10 mL of dry dichloromethane, 1-(3-aminopropyl)spiro[1H-indane-1,4'-piperidine] (53.0 mg, 0.216 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction mixture was stirred for another 1 h after addition of 2 mL of 6N HCl. The reaction mixture was basified with 10% aqueous KOH solution (pH = 9) and extracted into dichloromethane (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography (EtOAc/ MeOH, 4.5/0.5), giving 60.0 mg (100%) of the product as a syrup: ¹H NMR δ 1.52 (d, J=13.2 Hz, 2 H), 1.70-2.07 (m, 8 H), 2.12 (t, J=10.3 Hz, 2 H), 2.42 (s, 4 H), 2.86-2.91 (m, 3 H), 3.32-3.43 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 6.81 (br s, 1 H), 7.04-7.19 (m, 7 H), 8.82 (t, J=5.2 Hz, 1 H).
- To the free base (0.060 g, 0.108 mmol) in 4 mL of dichloromethane, 5 mL of 1 N HCl in ether was added, and the solution was concentrated under reduced pressure. Recrystallization from ether gave 0.070 g (100%) of the product as a white solid; m.p. 150-153 °C; Anal. Calcd.

-176-

for $C_{30}H_{36}F_2N_4O_6Cl$: C, 54.86; H, 5.53; N, 8.54. Found: C, 54.96; H, 5.57; N, 8.27.

5 **Example 33**

(+)-1,2,3,6-TETRAHYDRO-1-(N-[4-(3,4,5-TRIFLUORO)-PHENYL-PIPERIDIN-1-YL]PROPYL)CARBOXAMIDO-4-METHOXYMETHYL-6-(3,4-DIFLUOROPHENYL)-2-OXOPYRIMIDINE-5-CARBOXYLIC ACID METHYL ESTER: mp °C; $[\alpha]_D = +123.0$, (c = 0.15, MeOH); 1H NMR δ 1.70-1.82 (m, 6H), 1.97-2.08 (m, 2H), 2.40 (t, J=6.9 Hz, 2H), 2.74-2.87 (m, 1H), 3.01 (d, J=11.1 Hz, 2H), 3.29-3.40 (m, 2H), 3.49 (s, 3H), 3.71 (s, 3H), 4.69 (s, 2H), 6.68 (s, 1H), 6.88-6.95 (m, 2H), 7.05-7.11 (m, 2H), 7.15-7.22 (m, 1H), 7.71 (s, 1H), 8.90 (t, J=5.4 Hz, 1H).

15

Example 34

(+)-1,2,3,6-TETRAHYDRO-1-(N-[2-(S)-METHYL]-4-(2-NITROPHENYL)-PIPERAZIN-1-YL]PROPYL)-CARBOXAMIDO-4-METHYL-6-(3,4-DIFLUOROPHENYL)-2-EXO-PYRIMIDINE

20

(S)-(+)-3-METHYL-1-(2-NITROPHENYL)-PIPERAZINE: To a solution of 2-bromonitrobenzene (0.600 g, 3.00 mmol) in 1,4-dioxane (15 mL) was added (S)-(+)-2-methylpiperazine (0.500 g, 0.500 mmol) and powdered K_2CO_3 (15.0 mmol, 1.50 g) and the resulting suspension was heated at reflux for 10 h. After the suspension was cooled, it was filtered through a sintered glass funnel and the solvent was removed in vacuo. The resulting residue was purified by column chromatography (1/1 hexane/EtOAc followed by 4/1 EtOAc/MeOH), giving (S)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine as an orange oil (0.53 g, 80%).

25

30

(+)-1,2,3,6-TETRAHYDRO-1-(N-[2-(S)-METHYL]-4-(2-NITROPHEN

-177-

YL) PIPERAZIN-1YL] PROPYL)-CARBOXAMIDO-4-METHYL-6-(3,4-DIFLUOROPHENYL)-2-OXO-PYRIMIDINE: To a solution of (+)-1-(3-bromo-propylcarbamoyl)- 6-(3,4-difluorophenyl)-4-methyl-2-oxo-1,6-dihydro-pyrimidine-5- carboxylic acid methyl ester (0.200 g, 0.500 mmol) and (S)-(+)-3-methyl-1-(2-nitrophenyl)-piperazine (0.170 g, 0.750 mmol) in 20 mL of anhydrous acetone was added powdered K_2CO_3 (0.34 g, 3.5 mmol) and KI (0.07 g, 0.5 mmol) and the resulting suspension was heated at reflux temperature for 10 h. TLC indicated a new spot for the product (R_f = 0.3, 3/0.5 EtOAc/MeOH) and mostly the starting material. The suspension was cooled, filtered and the solvent was evaporated and the residue was purified by column chromatography (EtOAc/MeOH, 5/1). (+)-1,2,3,6-Tetrahydro-1-{N-[2-(S)-methyl)-4-(2-nitrophenyl)piperazin-1-yl]-propyl}-carboxamido-4-methyl-6-(3,4-difluorophenyl)-2-oxo-pyrimidine was obtained as yellow oil (0.030 g, 10% yield). The HCl salt was prepared by the addition of HCl in ether to a solution of the product in dichloromethane, followed by evaporation of the solvents; mp 150-153 °C; $[\alpha]_D = 58.3$ (c = 0.3, MeOH); 1H NMR (CD_3OD) δ 1.04 (d, J=6.0 Hz, 3 H), 1.71-1.78 (m, 2 H), 2.33-2.49 (m, 3 H), 2.42 (s, 3 H), 2.55-2.92 (m, 5 H), 3.00-3.10 (m, 3 H), 3.34-3.42 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 7.01-7.32 (m, 6 H), 7.46 (dt, J=0.7 Hz, J=8.4 Hz, 1 H), 7.74 (dd, J=1.5, 8.4 Hz, 1 H), 8.82 (t, J=3.9 Hz, 1 H). Anal calcd. for $C_{28}H_{33}N_6F_2O_6$ + 0.20 CH_2Cl_2 : C, 52.92; H, 5.26; N, 13.13. Found: C, 52.84; H, 5.68; N, 12.94.

30

Example 35

1,2,3,6-TETRAHYDRO-1{N-[4-(2'-METHYL-PHENYL) PIPERAZIN-1-YL]-PROPYL}-CARBOXAMIDO-4-METHYL-6-(3,4-DIFLUOROPHENYL)-2-OXO- PYRIMIDINE: The amine used was

-178-

4-(2'-methyl-phenyl)piperazine. ^1H NMR δ 1.75-1.80 (m, 2 H), 2.29 (s, 3 H), 2.42 (s, 3 H), 2.41-2.48 (m, 2 H), 2.58-2.62 (m, 4 H), 2.91-2.97 (m, 4 H), 3.35-3.42 (m, 2 H), 3.72 (s, 3 H), 6.71 (s, 1 H), 6.97-7.26 (m, 8 H), 8.81 (t, $J=3.9$ Hz, 1 H). The product was dissolved in ether and 1 N HCl in ether was added. The ether was evaporated, giving the dihydrochloride salt; mp 66-71 °C. Anal calcd. for $\text{C}_{28}\text{H}_{35}\text{N}_5\text{F}_2\text{O}_4 \cdot \text{Cl}_2 + 1.75$ acetone: C, 55.73; H, 6.40; N, 9.78. Found: C, 56.16; H, 6.29; N, 10.06.

10

Example 36

(+)-1,2,3,6-TETRAHYDRO-5-METHOXYCARBONYL-4-METHOXYMETHYL-2-OXO-1-{N-[3-(4-METHYL-4-PHENYL PIPERIDINE-1-YL)PROPYL]}-6-(3,4-DIFLUOROPHENYL) PYRIMIDINE: Hygroscopic; $[\alpha]_D = +82.1$ ($c = 0.31$, MeOH); ^1H NMR δ 1.14 (s, 3 H), 1.61-1.72 (m, 4 H), 2.03-2.08 (m, 2 H), 2.25 (t, $J=7.2$ Hz, 2 H), 2.30-2.42 (m, 4 H), 3.19-3.31 (m, 2 H), 3.40 (s, 3 H), 3.63 (s, 3 H), 4.60 (s, 2 H), 6.60 (s, 1 H), 6.97-7.29 (m, 8 H), 7.63 (br s, 1 H), 8.78 (t, $J=5.7$ Hz, 1 H). Anal calcd. for $\text{C}_{30}\text{H}_{37}\text{N}_4\text{O}_5\text{F}_2\text{Cl} + \text{CH}_2\text{Cl}_2$: C, 53.80; H, 5.68; N, 8.10. Found: C, 53.79; H, 6.03; N, 7.83.

15

20

EXAMPLE 37

5-(5-BUTYL-2-THIENYL) PYRIDO[2,3-d]PYRIMIDINE-2,4,7(1H,3H,8H)-TRIONE

25

General Procedure for the reaction of pyrimidine-3-carboxylic acid-4-nitrophenyl esters with amines:

A solution of substituted pyrimidine-3-carboxylic acid-4-nitrophenyl ester ((0.29 mmol) and a substituted 4-phenyl-1-(3-propylaminopiperidine (0.30 mmol) in 10 mL of anhydrous THF was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography.

10 **Example 38**

METHYL (4S)-3-[(3-[4-(3-AMINOPHENYL)-1-PIPERIDINYL] PROPYL)AMINO]CARBONYL]-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: ¹H NMR (400 MHz, CDCl₃) δ 7.80 (s, 1H), 7.22-7.02 (m, 2H), 6.95 (t, 2H, J=8.7 Hz), 6.63-6.44 (m, 4H), 4.56 (ABq, 2H), 3.62 (s, 3H), 3.33 (s, 3H), 3.32 (m, 4H), 2.96 (br s, 2H), 2.34 (t, 2H, J=7.5 Hz), 2.11-1.94 (m, 3H), 1.81-1.64 (m, 4H); ESMS m/e: 572.3 (M + H)⁺.

20

Example 39

The product was obtained according to the method described for Example 40.

25 METHYL (4S)-4-(3,4-DIFLUOROPHENYL)-3-[(3-[4-(3-[(METHOXYACETYL)AMINO]PHENYL)-1-PIPERIDINYL] PROPYL)AMINO]CARBONYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: 15.6 mg (69% yield); ¹H NMR (400 MHz, CDCl₃) δ 9.01 (s, 1H), 8.25 (s, 1H), 7.60 (s, 1H), 7.37 (d, 1H, J=7.2 Hz), 7.30-7.05 (m, 5H), 7.02 (d, 1H, J=8.0 Hz), 6.71 (s, 1H), 4.70 (s, 2H), 4.03 (s, 2H), 3.73 (s, 3H), 3.53 (s, 3H), 3.47 (s, 3H), 3.42-3.33 (m, 2H), 3.08 (br s, 2H), 2.49 (br s,

30

2H), 2.20 (s, 2H), 2.07 (br s, 1H), 1.97-1.75 (m, 4H);
ESMS m/e: 644.3 (M + H)⁺

Example 40

- 5 METHYL (4S)-4-(3,4-DIFLUOROPHENYL)-3-([3-(4-{3-[(3,3-DIMETHYLBUTANOYL)AMINO]PHENYL})-1-PIPERIDINYL)PROPYL]AMINO)CARBOXYL)-6-(METHOXYMETHYL)-2-
OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE
- 10 To the 20 ml vial was added methyl (4S)-3-([3-[4-(3-aminophenyl)-1-piperidinyl]propyl]amino)carbonyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (0.035 mmol), an acid
15 chloride or sulfonyl chloride (1.5 eq), N,N-diisopropylethylamine (5 eq) and dichloromethane (2 ml) at room temperature. The reaction mixture was stirred at room temperature for 24 h, at which time the TLC
analysis indicated the reaction was completed. The reaction mixture was concentrated to a small volume and
20 purified by preparative TLC (silica, 2000 microns, 95:5 = dichloromethane : methanol with 1% of isopropylamine) to give 5.6 mg of methyl (4S)-4-(3,4-difluorophenyl)-3-([3-(4-{3-[(3,3-dimethylbutanoyl)amino]phenyl})-1-piperidinyl]propyl]amino)carbonyl)-6-(methoxymethyl)-2-
25 oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate: 24.6% yield; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (s, 1H), 7.26 (d, 1H, J=8.3 Hz), 7.15-7.02 (m, 5H), 6.88 (d, 1H, J=8.3 Hz), 6.55 (s, 1H), 4.56 (ABq, 2H), 3.62 (s, 3H), 3.32 (s, 3H), 3.25 (t, 4H, J=9.0 Hz), 2.99 (d, 2H, J=10.8
30 Hz), 2.49-2.37 (m, 3H), 2.08 (t, 2H, J=11.7 Hz), 1.78-1.65 (m, 14H); ESMS m/e: 670.4 (M + H)⁺.

Example 41

The product was obtained according to the method described for methyl (4S)-4-(3,4-difluorophenyl)-3-([3-(4-{3-[(3,3-dimethylbutanoyl)amino]phenyl}-1-piperidinyl)propyl]amino)carbonyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate.

METHYL (4S)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-
OXO-3-([3-(4-{3-(PROPIONYLAMINO)PHENYL}-1-
10 PIPERIDINYL)PROPYL]AMINO)CARBONYL)-1,2,3,4-TETRAHYDRO-5-
PYRIMIDINECARBOXYLATE: 9.9 mg (45% yield) δ ^1H NMR (400
MHz, CDCl_3) δ 7.36 (s, 1H), 7.28 (d, 1H, $J=8.0$ Hz), 7.16-
7.02 (m, 5H), 6.86 (d, 1H, $J=7.6$ Hz), 6.54 (s, 1H), 4.56
(ABq, 2H), 3.62 (s, 3H), 3.32 (s, 3H), 3.27-3.19 (m,
15 4H), 2.95 (d, 2H, $J=10.3$ Hz), 2.41 (m, 1H), 2.34 (t, 2H,
 $J=7.7$ Hz), 2.28 (q, 2H, $J=7.6$ Hz), 2.01 (t, 2H, $J=11.1$
Hz), 1.73-1.64 (m, 8H); ESMS m/e : 628.4 ($M + H$) $^+$

Example 42

20 The product was obtained according to the method
described for methyl (4S)-4-(3,4-difluorophenyl)-3-([3-(4-{3-[(3,3-dimethylbutanoyl)amino]phenyl}-1-
piperidinyl)propyl]amino)carbonyl)-6-(methoxymethyl)-2-
oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate.

25 METHYL (4S)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-3-
([3-(4-{3-[(3-METHYLBUTANOYL)AMINO]PHENYL}-1-
PIPERIDINYL)PROPYL]AMINO)CARBONYL)-2-
OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: 10.4 mg (45% yield)
30 δ ^1H NMR (400 MHz, CDCl_3) δ 7.36 (s, 1H), 7.28 (d, 1H,
 $J=7.9$ Hz), 7.16-7.03 (m, 5H), 6.88 (d, 1H, $J=7.4$ Hz),
6.56 (s, 1H), 4.56 (ABq, 2H), 3.62 (s, 3H), 3.32 (s,
3H), 3.25 (t, 4H, $J=6.7$ Hz), 2.98 (d, 2H, $J=11.1$ Hz),

182

2.43 (m, 1H), 2.38 (t, 2H, J=7.5 Hz), 1.13 (d, 2H, J=7.5 Hz), 2.10-2.01 (m, 2H), 1.75-1.64 (m, 6H), 0.91 (d, 6H, J=5.8 Hz); ESMS m/e: 656.4 (M + H)⁺

5 **Example 43**

The product was obtained according to the method described for methyl (4S)-4-(3,4-difluorophenyl)-3-({[3-(4-{3-[(3,3-dimethylbutanoyl)amino]phenyl}-1-piperidinyl)propyl]amino}carbonyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate.

METHYL (4S)-4-(3,4-DIFLUOROPHENYL)-3-({[3-(4-{3-(ISOBUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)AMINO]CARBONYL)-6-(METHOXYMETHYL)-2-
15 OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: 16.4 mg
(73% yield) δ ¹H NMR (400 MHz, CDCl₃) δ 7.37 (s, 1H), 7.28 (d, 1H, J=7.3 Hz), 7.16-7.01 (m, 5H), 6.88 (d, 2H, J=7.3 Hz), 6.54 (s, 1H), 4.56 (ABq, 2H), 3.62 (s, 3H), 3.32 (s, 3H), 3.25 (t, 2H, J=6.8 Hz), 3.23-3.18 (m, 2H), 3.03
20 (d, 2H, J=11.7 Hz), 2.57-2.48 (m, 1H), 2.43 (t, 2H, J=8.0 Hz), 2.14 (t, 2H, J=9.4 Hz), 1.8-1.65 (m, 5H), 1.09 (d, 6H, J=6.3 Hz); ESMS m/e: 642.4 (M + H)⁺

Example 44

25 The product was obtained according to the method described for methyl (4S)-4-(3,4-difluorophenyl)-3-({[3-(4-{3-[(3,3-dimethylbutanoyl)amino]phenyl}-1-piperidinyl)propyl]amino}carbonyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate.

30

METHYL (4S)-3-({[3-(4-{3-(BUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)AMINO]CARBONYL)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-oxo-1,2,3,4-

183

TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: 14.7 mg (65.5%
yield) δ ^1H NMR (400 MHz, CDCl_3) δ 7.38 (s, 1H), 7.26 (s,
1H), 7.17-6.99 (m, 5H), 6.87 (s, 1H), 6.55 (s, 1H), 4.56
(ABq, 2H), 3.63 (s, 3H), 3.33 (s, 3H), 3.28-3.17 (m,
5 6H), 3.0 (br s, 2H), 2.51-2.36 (m, 3H), 2.25 (t, 2H,
 $J=5.0$ Hz), 2.10 (br s, 2H), 1.8-1.56 (m, 6H), 0.90 (t,
3H, $J=5.0$ Hz); ESMS m/e : 642.4 ($M + H$) $^+$.

Example 45

10 (4R)-N-(3-{4-[3-(BUTYRYLAMINO)PHENYL]-1-
PIPERIDINYL)PROPYL}-4-(3,4-DIFLUOROPHENYL)-6-
(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-
PYRIMIDINECARBOXAMIDE

15 Method:

(4R)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-
1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid: A
stirred mixture of one mole equivalent of methyl (4R)-4-
20 (3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-
tetrahydro-5-pyrimidinecarboxylate (10.0 g, 32.0 mmol)
and lithium hydroxide (2 equivalents, 1.53 g, 64.0 mol)
in H_2O -THF (2:1, 300 mL) was heated at reflux temperature
for 1 h. The reaction mixture was concentrated,
25 dissolved in water, washed with ethyl acetate and
acidified (1 N HCl) to pH 3-4 (pH paper). The
precipitated product was collected, washed with water
and dried under reduced pressure to give the desired
product in 90% yield.

30

(4R)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-N-[3-(4-
(3-NITROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIDINYL)PROPYL]-2-
OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXAMIDE: A

solution of (4R)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylic acid (1.2 eq), EDC (1.5 Eq.), N-methylmorpholine (2.0 Eq.) in dichloromethane was
5 stirred at room temperature for 15 minutes, followed by addition of 3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)-1-propanamine (1.0 eq.) to the reaction mixture. The resulting solution was stirred for 18 hours, concentrated and chromatographed on silica to
10 give (4R)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-N-[3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)propyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide.

(4R)-N-{3-[4-(3-AMINOPHENYL)-1-PIPERIDINYL]PROPYL}-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXAMIDE: A mixture of (4R)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-N-[3-(4-(3-nitrophenyl)-3,6-dihydro-1(2H)-pyridinyl)propyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide, 10% Pd/C in
20 ethanol was hydrogenated (balloon method) for 2 days. The reaction mixture was filtered through Celite 545, washed with ethanol and concentrated to give the desired product.

(4R)-N-(3-{4-[3-(BUTYRYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXAMIDE: Into a 20 mL vial was added (4R)-N-{3-[4-(3-aminophenyl)-1-piperidinyl]propyl}-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide (0.040 mmol), acid
30 chloride (1.5 eq) and N,N-diisopropylethylamine (5.0 eq) in 2.0 mL of dichloromethane at room temperature. After

24 hrs, the reaction mixture was concentrated in vacuo and purified by preparative TLC (silica, 2000 microns, 95:5 = dichloromethane : methanol with 1% of isopropylamine) to give 9.2 mg (45% yield) of the
5 desired product: ^1H NMR (400 MHz, CD_3OD) δ 7.49 (s, 1H), 7.25 (d, 1H, $J=7.6$ Hz), 7.20-7.02 (m, 5H), 6.91 (d, 1H, $J=8$ Hz), 5.29 (s, 1H), 4.24 (ABq, 2H), 3.30 and 3.24 (two s, 3H), 3.46-3.12 (m, partially hidden by three s, 4H), 2.74 (br s, 4H), 2.25 (t, 2H, $J=8.2$ Hz), 2.04-1.69
10 (m, 7H), 1.63 (sextet, 2H, $J=7.4$ Hz), 0.91 (t, 3H, 7.4 Hz); ESMS m/e : 584.4 ($M + H$) $^+$.

Example 46

The product was obtained according to the method
15 described for (4R)-N-(3-{4-[3-(butyrylamino)phenyl]-1-piperidinyl}propyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide.

20 (4R)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-2-OXO-N-(3-{4-[3-(PROPIONYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXAMIDE: 5.6 mg (24.6% yield); ^1H NMR (400 MHz, CD_3OD) δ 7.56 (s, 1H), 7.35 (d, 1H, $J=6.9$ Hz), 7.3-7.03 (m, 4H), 7.17 (br s, 1H), 6.99 (d, 1H, $J=7.0$ Hz), 5.45 (s, 1H), 4.33 (ABq, 2H), 3.41 (s, 3H), 3.37-3.23 (m, partially hidden, 4H),
25 2.8 (br s, 4H), 2.39 (d, 2H, $J=9.3$ Hz), 2.14-1.78 (m, 7H), 1.21 (t, 3H, $J=7.6$ Hz); ESMS m/e : 570.4 ($M + H$) $^+$.

Example 47

30 The product was obtained according to the method described for (4R)-N-(3-{4-[3-(butyrylamino)phenyl]-1-piperidinyl}propyl)-4-(3,4-difluorophenyl)-6-

186

(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide.

(4R)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-N-[3-(4-
5 {3-[(3-METHYLBUTANOYL)AMINO]PHENYL}-1-
PIPERIDINYL)PROPYL]-2-oxo-1,2,3,4-tetrahydro-5-
PYRIMIDINECARBOXAMIDE: 11.1 mg (46% yield); ¹H NMR (400
MHz, CD₃OD) δ 7.81 (d, 1H, J=8.5 Hz), 7.6 (s, 1H), 7.55 (s,
1H), 7.36 (br s, 1 H), 7.31-7.17 (m, 3H), 7.01 (t, 1H,
10 J=6.7 Hz) 6.64-6.61 (m, 1H), 5.45 (br s, 1H), 4.32 (ABq,
2H), 3.94 and 3.87 (two s, 3H), 3.42-3.12 (m, partially
hidden, 2H), 3.1 (br s, 2H), 3.0 (t, 2H, J=11.1 Hz),
2.79-2.57 (m, 4H), 2.27-1.73 (m, 8H), 1.19 and 1.01 (two
d, 6H, J=6.6 Hz); ESMS m/e: 598.4 (M + H)⁺.

15

Example 48

The product was obtained according to the method
described for (4R)-N-(3-{4-[3-(butyrylamino)phenyl]-1-
piperidinyl}propyl)-4-(3,4-difluorophenyl)-6-
20 (methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-
pyrimidinecarboxamide.

(4R)-4-(3,4-DIFLUOROPHENYL)-6-(METHOXYMETHYL)-N-[3-(4-
{3-[(2-METHYLBUTANOYL)AMINO]PHENYL}-1-
25 PIPERIDINYL)PROPYL]-2-oxo-1,2,3,4-tetrahydro-5-
PYRIMIDINECARBOXAMIDE: 6.7 mg (28% yield); ¹H NMR (400
MHz, CD₃OD) δ 7.59 (s, 1H), 7.35 (br s, 1H), 7.3-7.2 (m,
3H), 7.17 (br s, 1H), 7.01 (d, 1H, J=6.8 Hz), 5.45 (s,
1H), 4.33 (ABq, 2H), 3.39 (s, 3H), 3.29 (m, 2H), 2.84
30 (br s, 4H), 2.42 (m, 1H), 2.14-1.78 (m, 9H), 1.7 (m,
1H), 1.49 (m, 1H), 1.20 (d, 3H, J=6.7 Hz), 0.95 (t, 3H,
J=6.6 Hz); ESMS m/e: 598.4 (M + H)⁺.

Example 49

The product was obtained according to the method described for (4R)-N-(3-{4-[3-(butyrylamino)phenyl]-1-piperidinyl}propyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide.

(4R)-4-(3,4-DIFLUOROPHENYL)-N-[3-(4-{3-[(3,3-DIMETHYLBUTANOYL)AMINO]PHENYL}-1-PIPERIDINYL)PROPYL]-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXAMIDE: 1.1 mg (4.4% yield); ¹H NMR (400 MHz, CD₃OD) δ 7.6-6.91 (m, 7H), 5.43 (s, 1H), 4.31 (ABq, 2H), 3.40 (s, 3H), 3.27-1.26 (m, 17 H), 1.09 (s, 9H); ESMS m/e: 612.4 (M + H)⁺.

Example 50

The product was obtained according to the method described for (4R)-N-(3-{4-[3-(butyrylamino)phenyl]-1-piperidinyl}propyl)-4-(3,4-difluorophenyl)-6-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxamide.

(4R)-4-(3,4-DIFLUOROPHENYL)-N-(3-(4-{3-(ISOBUTYRYLAMINO)PHENYL}-1-PIPERIDINYL)PROPYL)-6-(METHOXYMETHYL)-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXAMIDE: 12.7 mg (54% yield); ¹H NMR (400 MHz, CD₃OD) δ 7.59(s, 1H), 7.36 (d, 1H, J=8.6 Hz), 7.31-7.07 (m, 4H), 7.01 (d, 1H, J=6.5 Hz), 5.39 (s, 1H), 4.34 (ABq, 2H), 3.35 (s, 3H), 3.33-3.19 (m, partially hidden, 2H), 3.08-2.72 (m, 4H), 2.63 (t, 2H, J=7.2 Hz), 2.14-1.82 (m, 8H), 1.19 (d, 6H, J=6.9 Hz); ESMS m/e: 584.4 (M + H)⁺.

Example 51

The synthetic method is the same as described for the synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

5-ACETYL-N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-4-METHYL-2-OXO-6-(3,4,5-TRIFLUOROPHENYL)-3,6-DIHYDRO-1(2H)-PYRIMIDINECARBOXAMIDE: 14.5 mg (46% yield); ¹H NMR (400 MHz, CDCl₃) δ 9.56 (s, 1H), 9.20 (s, 1H), 8.21 (s, 1H), 7.52 (s, 1H), 7.18 (t, 1H, J=7.8 Hz), 7.07-6.75 (m, 5H), 3.59-3.37 (m, 1H), 3.48-3.38 (m, 1H), 3.08 (br s, 2H), 2.57-2.39 (m, 5H), 2.25 (s, 3H), 2.21 (s, 3H), 2.19-1.59 (m, 9H); ESMS m/e: 586.3 (M + H)⁺; Anal. Calc. for C₃₀H₃₄F₃N₅O₄+0.1CHCl₃: C, 60.50; H, 5.75; N, 11.72. Found: C, 60.59; H, 5.40; N, 11.73.

Example 52

The synthetic method is the same as described for the synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

BENZYL 3-[[3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)AMINO]CARBONYL)-4-(2,4-DIFLUOROPHENYL)-6-ETHYL-2-OXO-1,2,3,4-TETRAHYDRO-5-PYRIMIDINECARBOXYLATE: 14.8 mg (41% yield); ¹H NMR (400 MHz, CDCl₃) δ 9.05 (br s, 1H), 8.14 (s, 1H), 7.47 (s, 1H),

189

2.17-1.88 (m, 3H), 1.77-1.58 (m, 3H), 1.19 (t, 3H, J=7.5 Hz); ESMS m/e: 674.4 (M + H)⁺.

Example 53

5 The synthetic method is the same as described for the synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

10 N-(3-{4-[3-(ACETYLAMINO) PHENYL]-1-PIPERIDINYL} PROPYL)-4-(1,3-BENZODIOXOL-5-YL)-2,5-DIOXO-1,2,5,7-TETRAHYDROFURO[3,4-D]PYRIMIDINE-3(4H)-CARBOXAMIDE: 8.75 mg (28% yield); ¹H NMR (400 MHz, CDCl₃) δ 9.81 (s, 1H), 8.14 (s, 1H), 7.53 (s, 1H), 7.21 (t, 1H, J=7.7 Hz), 6.99 (d, 1H, J=7.7 Hz), 6.91-6.7 (m, 4H), 6.42 (s, 1H), 5.9 (s, 2H), 4.75 (s, 2H), 3.61-3.5 (m, 1H), 3.37-3.27 (m, 1H), 3.08 (br s, 2H), 2.56-2.40 (m, 3H), 2.18 (s, 3H), 2.16-1.85 (m, 4H), 1.78-1.6 (m, 5H); ESMS m/e: 576.3 (M + H)⁺.

15

20

Example 54

The synthetic method is the same as described for the synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-oxazolidine-3-carboxamide.

25

METHYL 1-{[(3-{4-[3-(ACETYLAMINO) PHENYL]-1-PIPERIDINYL} PROPYL) AMINO] CARBONYL}-2-[(4-METHOXYBENZYL) SULFANYL]-4-METHYL-6-(4-NITROPHENYL)-1,6-DIHYDRO-5-PYRIMIDINECARBOXYLATE: 10.1 mg (26% yield); ¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, 2H, J=7.5 Hz), 7.53 (br s, 1H), 7.44-7.27 (m, 6H), 7.14 (d, 2H, J=8.5 Hz), 6.99 (d, 1H, J=7.6 Hz), 6.75 (d, 2H, J=8.5 Hz), 6.2 (s, 1H), 4.23 .

30

190

(ABq, 2H), 3.78 (s, 3H), 3.7 (s, 3H), 3.58-3.48 (m, 1H)
3.37-3.26 (m, 2H), 3.04 (m, 2H), 2.61-2.43 (m, 3H), 2.41
(s, 3H), 2.16 (s, 3H), 2.15-1.64 (m, 8H); ESMS m/e:
729.3 (M + H)⁺.

5

Example 55

The synthetic method is the same as described for the
synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-
piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-
oxazolidine-3-carboxamide.

10

N-(3-{4-[3-(ACETYLAMINO)PHENYL]-1-PIPERIDINYL}PROPYL)-4-
(2,1,3-BENZOXADIAZOL-5-YL)-2,5-DIOXO-1,2,5,7-
TETRAHYDROFURO[3,4-D]PYRIMIDINE-3(4H)-CARBOXAMIDE: 7.7
mg (12% yield); ¹H NMR (400 MHz, CDCl₃) δ 7.97-6.83 (m,
7H), 6.49 (s, 1H), 5.51 (s, 1H), 3.43-2.02 (m, 17 H),
1.82 (s, 3H); ESMS m/e: 574.3 (M + H)⁺.

15

Example 56

The synthetic method is the same as described for the
synthesis of (4S)-N-(3-{4-[3-(acetylamino)phenyl]-1-
piperidinyl}propyl)-4-(3,5-difluorophenyl)-2-oxo-1,3-
oxazolidine-3-carboxamide.

20

METHYL (4S)-3-{[(3-{4-[3-(ACETYLAMINO)PHENYL]-1-
PIPERIDINYL}PROPYL)AMINO]CARBONYL}-4-(3,4-
DIFLUOROPHENYL)-6-METHYL-2-OXO-1,2,3,4-TETRAHYDRO-5-
PYRIMIDINECARBOXYLATE: 16.6 mg (52% yield); ¹H NMR (400
MHz, CDCl₃) δ 9.55 (br s, 1H), 9.07 (s, 1H), 8.19 (s,
1H), 7.54 (s, 1H), 7.25-6.98 (m, 4H), 6.95 (d, 1H, J=8.0
Hz), 6.81 (d, 1H, J=7.5 Hz), 6.69 (s, 1H), 3.70 (s, 3H),
3.57-3.34 (m, 2H), 3.06 (t, 2H, J=11.6 Hz), 2.47 (t, 2H,
J=8.1 Hz), 2.42 (s, 3H), 2.20 (s, 3H), 2.18-1.61 (m,

30

191

9H); ESMS m/e: 584.3 (M + H)⁺; Anal. Calc. for
C₃₀H₃₅F₂N₅O+0.25CHCl₃: C, 59.23; H, 5.79; N, 11.42. Found:
C, 59.61; H, 5.31; N, 11.48.

-192-

Peptide Synthesis:

Abbreviations: Fmoc: 9-Fluorenyloxycarbonyl-; Trityl:
5 triphenylmethyl-; tBu-: tertiary butyl ester; OtBu-:
tertiary butyl ether; Ng: N-guanidinyll; Nin: N-Indole;
MBHA : methylbenzhydramine; DMF: N,N-dimethylformamide;
NMP: N-Methylpyrrolidinone; DIEA: diisopropylethyl
amine; TFA: trifluoroacetic acid.

10

Small scale peptide syntheses were performed either
manually, by using a sintered glass column with argon
pressure to remove solvents and reagents, or by using an
Advanced ChemTech 396-9000 automated peptide synthesizer
15 (Advanced ChemTech, Louisville, KY). Large scale peptide
syntheses were performed on a CS Bio 536 (CS Bio Inc.,
San Carlos, CA). Fmoc-Alanine-OH,

Fmoc-Cysteine(Trityl)-OH, Fmoc-Aspartic acid(tBu)-OH,
Fmoc-Glutamic acid(tBu)-OH, Fmoc-Phenylalanine-OH,
20 Fmoc-Glycine-OH, Fmoc-Histidine(Trityl)-OH,
Fmoc-Isoleucine-OH, Fmoc-Lysine(Boc)-OH, Fmoc-Leucine-OH,
Fmoc-Methionine-OH, Fmoc-Asparagine(Trityl)-OH,
Fmoc-Proline-OH, Fmoc-Glutamine(Trityl)-OH,
Fmoc-Arginine(Ng-2,2,4,6,7-Pentamethyldihydrobenzofuran-5
25 -sulfonyl)-OH, Fmoc-Serine(OtBu)-OH,
Fmoc-Threonine(OtBu)-OH, Fmoc-Valine-OH,
Fmoc-Tryptophan(NinBoc)-OH, Fmoc-Tyrosine(OtBu)-OH,
Fmoc-Cyclohexylalanine-OH, and Fmoc-Norleucine , Fmoc
-O-benzyl-phosphotyrosine were used as protected amino
30 acids. Any corresponding D-amino acids had the same
side-chain protecting groups, with the exception of
Fmoc-D-Arginine, which had a Ng-2,2,5,7,8-pentamethyl-
chroman-6-sulfonyl protecting group.

35

Peptides with C-terminal amides were synthesized on solid

-193-

phase using Rink amide-MBHA resin. The Fmoc group of the Rink Amide MBHA resin was removed by treatment with 30% piperidine in DMF for 5 and 30 minutes respectively. After washing with DMF (3 times), methanol (2 times) and DMF/NMP (3 times), the appropriate Fmoc-protected amino acid (4 eq.) was coupled for 2 hours with HBTU or HATU (4eq.) as the activating agent and DIEA (8eq.) as the base. In manual syntheses, the ninhydrin test was used to test for complete coupling of the amino acids. The Fmoc groups were removed by treatment with 30% piperidine in DMF for 5 and 30 minutes respectively. After washing with DMF (3 times), methanol (2 times) and DMF/NMP (3 times), the next Fmoc-protected amino acid (4 eq.) was coupled for 2 hours with HBTU or HATU (4eq.) as the activating agent and DIEA (8eq.) as the base. This process of coupling and deprotection of the Fmoc group was continued until the desired peptide was assembled on the resin. The N-terminal Fmoc group was removed by treatment with 30% piperidine in DMF for 5 and 30 minutes respectively. After washing with DMF (3 times), methanol (2 times), the resin(s) was vacuum dried for 2 hours. Cleavage of the peptide-on-resin and removal of the side chain protecting groups was achieved by treating with TFA : ethanedithiol : thioanisole: m-cresol : water : triisopropylsilane : phenol, 78/5/3/3/3/5/3 (5 mL per 100 mg resin) for 2.5-3 hours. The cleavage cocktail containing the peptide was filtered into a round bottom flask and the volatile liquids were removed by rotary evaporation at 30-40 °C. The peptides were precipitated with anhydrous ether, collected on a medium-pore sintered glass funnel by vacuum filtration, washed with ether and vacuum dried.

Peptides with C-terminal acids were synthesized using 2-chlorotrityl chloride resin. The first amino acid was

-194-

attached to the resin by dissolving 0.6-1.2eq. of the appropriate Fmoc-protected amino acid described above in dichloromethane (a minimal amount of DMF was added to facilitate the dissolution, if necessary). To this was
5 added DIEA (4 eq. Relative to the Fmoc-amino acid) and the solution was added to the resin and shaken for 30-120 minutes. The solvents and the excess reagents were drained and the resin was washed with dichloromethane / methanol / DIEA (17/2/1) (3 times), dichloromethane (3
10 times), DMF (2 times), dichloromethane (2 times), and vacuum dried. The process of deprotection of the Fmoc group and coupling the appropriate Fmoc-protected amino acid was continued as described above, until the desired, fully protected peptide was assembled on the resin. The
15 process for removal of the final Fmoc group and the cleavage and deprotection of the peptides was the same as described above for the peptides with C-terminal amides.

Purification of the peptides was achieved by preparative
20 high performance column chromatography (HPLC), using a reverse-phase C-18 column (25 x 250mm) (Primesphere or Vydac) with a gradient of acetonitrile (0.1% TFA) in water (0.1% TFA). The general gradient was from 10%-90% acetonitrile in water over 40 minutes. The fractions
25 corresponding to each peak on the HPLC trace was collected, freeze dried and analyzed by electrospray mass spectrometry. The fraction having the correct mass spectral data corresponding to the desired peptide was then further analyzed by amino acid analysis, if
30 necessary. All purified peptides were tested for homogeneity by analytical HPLC using conditions similar to that described above, but by using a 2.5x250 mm analytical column, and generally were found to have >95%
35 purity.

-195-

References:

See our published dihydropyrimidinone and oxazolidinone
patents as references for the synthesis of the templates
5 and the piperidines.

Also, for the synthesis of the aminopropyl piperidines
and the templates, see:

10 Lagu, Bharat, et al., Design and synthesis of novel α_{1a}
adrenoceptor-selective antagonists. 3. Approaches to
eliminate opioid agonist metabolites by using substituted
phenylpiperazine side chains. *J. Med. Chem.* (1999),
42(23), 4794-4803. CODEN: JMCMAR ISSN:0022-2623. CAN
132:78527 AN 1999:680975 CAPLUS

15 Dhar, T. G. Murali, et al., Design and Synthesis of
Novel α_{1a} Adrenoceptor-Selective Antagonists. 2.
Approaches To Eliminate Opioid Agonist Metabolites via
Modification of Linker and 4-Methoxycarbonyl-4-phenyl
20 piperidine Moiety. *J. Med. Chem.* (1999), 42(23),
4778-4793. CODEN: JMCMAR ISSN:0022-2623. CAN 132:18483
AN 1999:680971 CAPLUS

25 Nagarathnam, Dhanapalan, et al., Design and Synthesis of
Novel α_{1a} Adrenoceptor-Selective Antagonists. 1.
Structure-Activity Relationship in Dihydropyrimidinones.
J. Med. Chem. (1999), 42(23), 4764-4777. CODEN:
JMCMAR ISSN:0022-2623. CAN 132:18482 AN 1999:680967
CAPLUS

30 Wong, Wai C., et al., Design and Synthesis of Novel α_{1a}
Adrenoceptor-Selective Antagonists. 4. Structure-Activity
Relationship in the Dihydropyrimidine Series. *J. Med.*
Chem. (1999), 42(23), 4804-4813. CODEN: JMCMAR

-196-

ISSN:0022-2623. CAN 132:30317 AN 1999:680947 CAPLUS

- Marzabadi, Mohammad R., et al., Design and synthesis of novel dihydropyridine alpha-1A antagonists. *Bioorg. Med. Chem. Lett.* (1999), 9(19), 2843-2848. CODEN: BMCLE8 ISSN:0960-894X. CAN 132:44482 AN 1999:662323 CAPLUS
- 5
- Wong, Wai C., et al., Alpha-1a adrenoceptor selective antagonists as novel agents for treating benign prostatic hyperplasia. Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (1999), MEDI-156. CODEN: 67GHA6 AN 1999:92669 CAPLUS
- 10
- Nagarathnam, D., et al., Design, synthesis and evaluation of dihydropyrimidinones as alpha-1a selective antagonists: 7. Modification of the piperidine moiety into 4-aminocyclohexane; identification and structure-activity relationship of SNAP 6991 analogs. Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (1999), MEDI-110. CODEN: 67GHA6 AN 1999:92624 CAPLUS
- 15
- 20
- Lagu, Bharat, et al., Heterocyclic substituted oxazolidinones for use as selective antagonists for human a 1A receptors. *PCT Int. Appl.* (1998), 258 pp. CODEN: PIXXD2 WO 9857940 A1 19981223 CAN 130:81508 AN 1999:9823 CAPLUS
- 25
- Wong, Wai C., et al., Preparation of piperidinylpropyl aminocarbonyldihydropyrimidones and related compounds as selective adrenergic a 1A receptor antagonists. *PCT Int. Appl.* (1998), 314 pp. CODEN: PIXXD2 WO 9851311 A2 19981119 CAN 130:25077 AN 1998:764290
- 30
- 35
- CAPLUS

-197-

Nagarathnam, Dhanapalan, et al., Design and synthesis of novel α_1 adrenoceptor-selective dihydropyridine antagonists for the treatment of benign prostatic hyperplasia. *J. Med. Chem.* (1998), 41(26),
5 5320-5333. CODEN: JMCMAR ISSN:0022-2623. CAN
130:110137 AN 1998:742998 CAPLUS

For the general procedure for Pd coupling of vinyl triflate and bononic acids or tributyl tin reagents: See,
10 Wuston, Wise *Synthesis* 1991, 993)

(For Typical References, See:Schroeter, G. *Ber.* (1909) 42, 3356; and Allen, C.F.H.; Bell, A. *Org. Syn. Coll. Vol. 3*, (1955) 846).

15 For the preparation of the ether N-[4-(benzo-4',5'[H]-furanpiperidine refer to W.E.Parham et al, *J. Org. Chem.* (1976) 41, 2268.

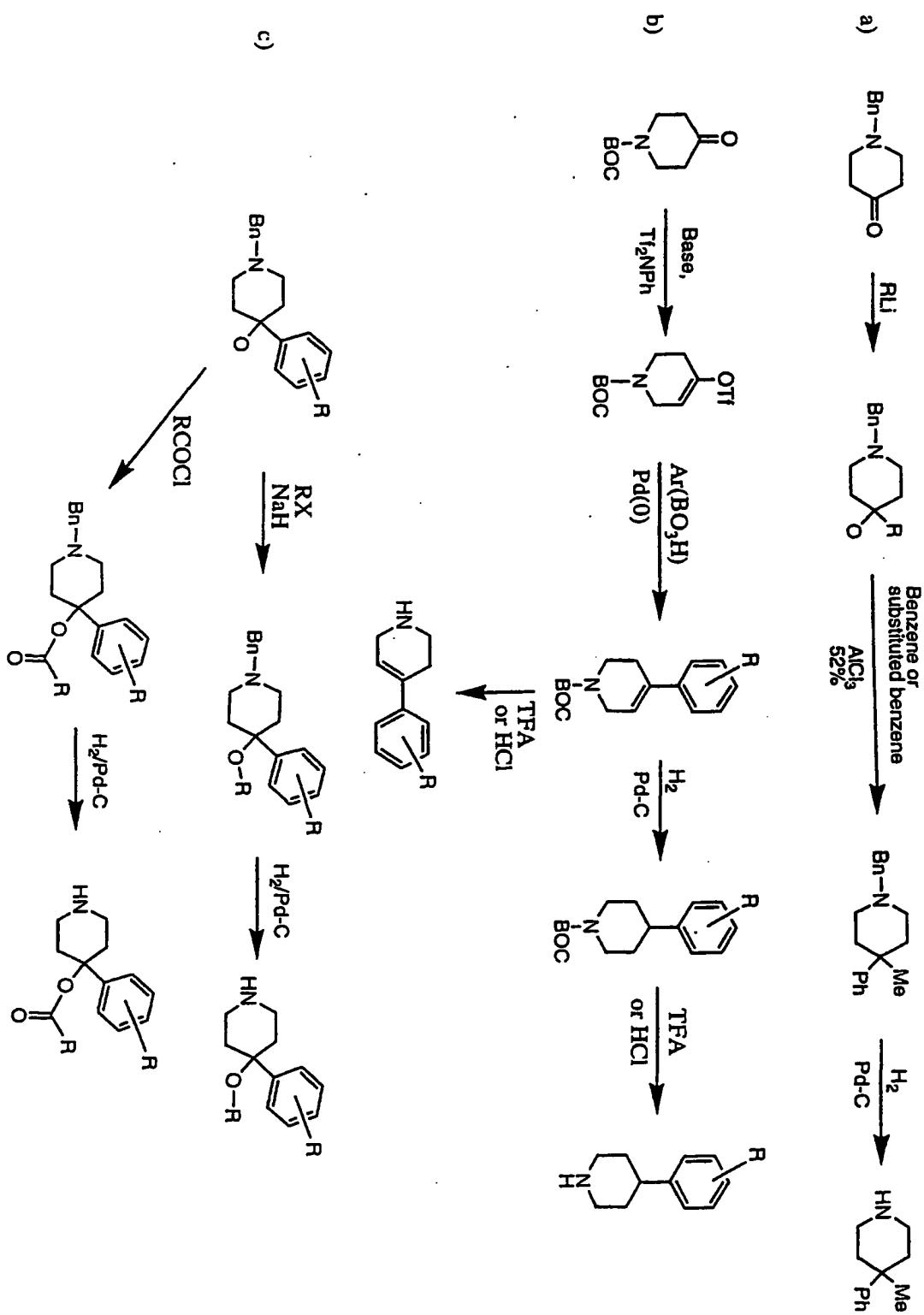
20 For the preparation of the ether piperidine precursor of Example 20, refer to W.E.Parham et al, *J. Org. Chem.* (1976) 41, 2268.

25 For the preparation of the indane piperidine precursor of Example 21, refer to M.S.Chambers *J. Med. Chem.* (1992) 35, 2033.

30 For the preparation of the piperidine precursor of Example 23, (K.Hashigaki et al. *Chem.Pharm.Bull.* (1984) 32, 3568.)

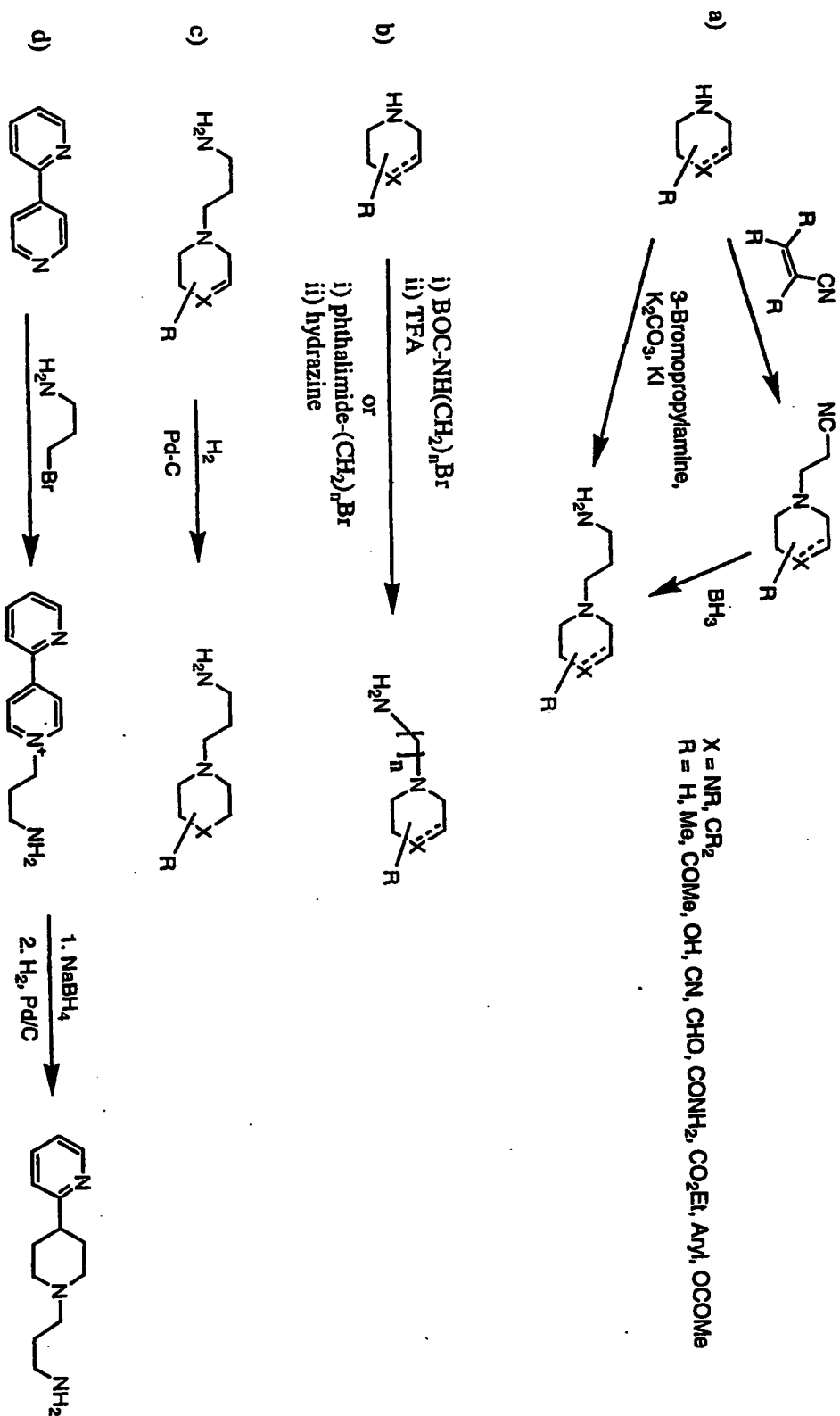
For the preparation of the piperidine precursor of Example 32, spiro[1H-indane-1,4'-piperidine], refer to M.S.Chambers et al. *J. Med. Chem.* (1992) 35, 2033.)

Scheme 1. Synthesis of Precursor Compounds



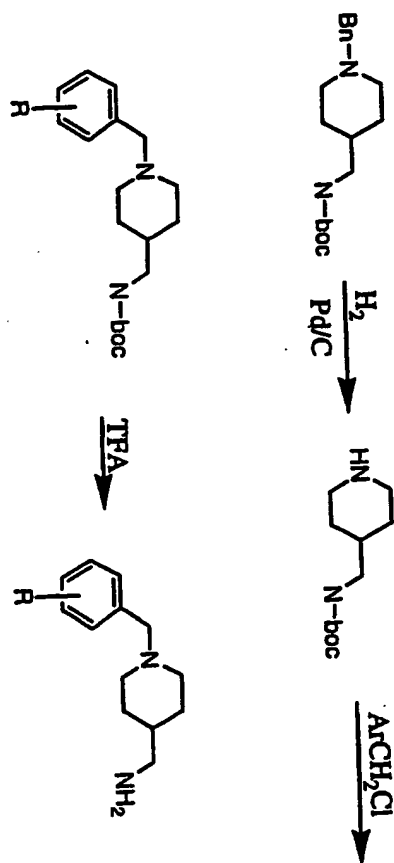
-199-

Scheme 2. Synthesis of Precursor Compounds



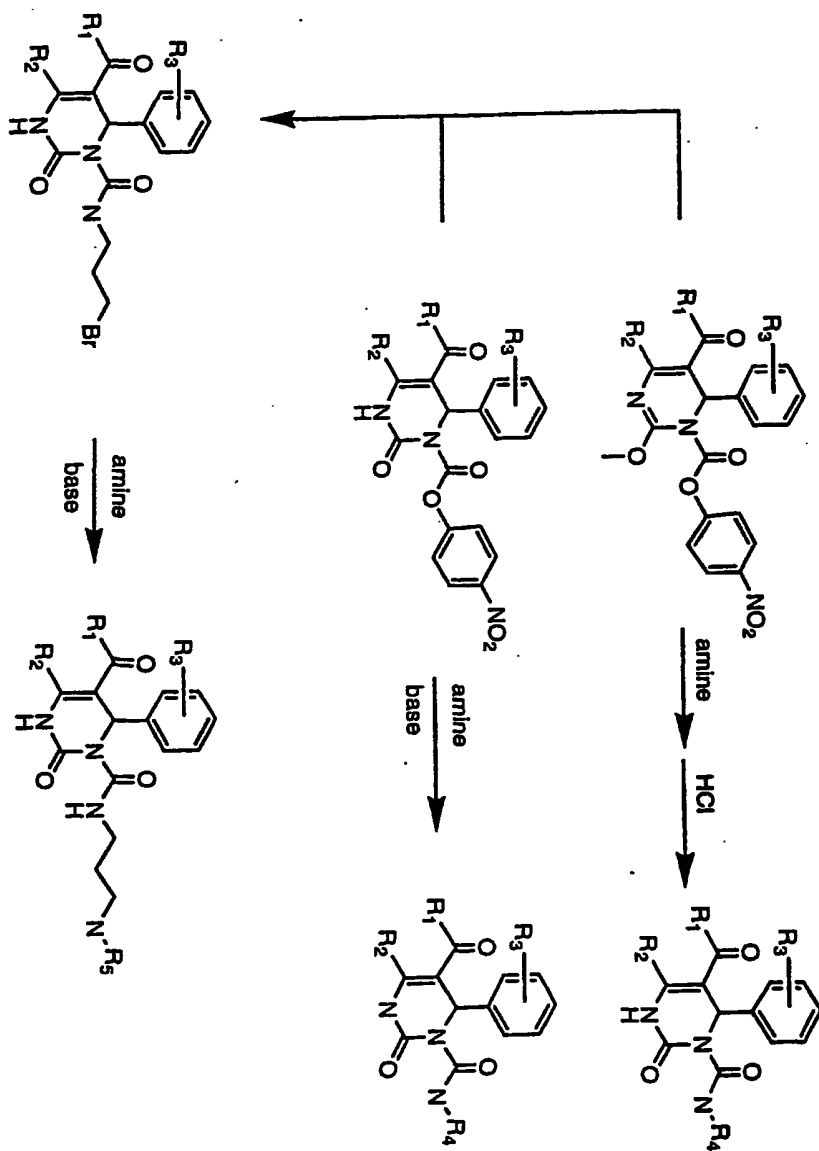
-200-

Scheme 3. Synthesis of Precursor Compounds



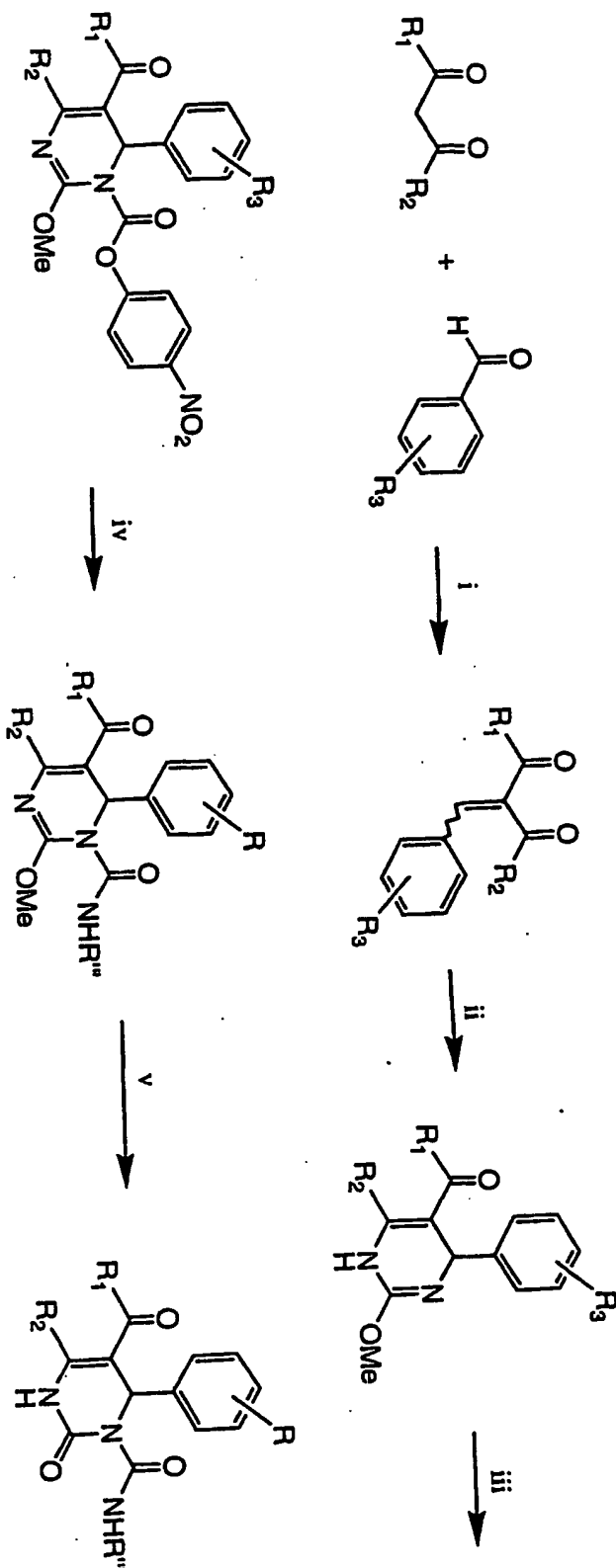
-201-

Scheme 4. Synthesis of Various Dihydropyrimidinones



-202-

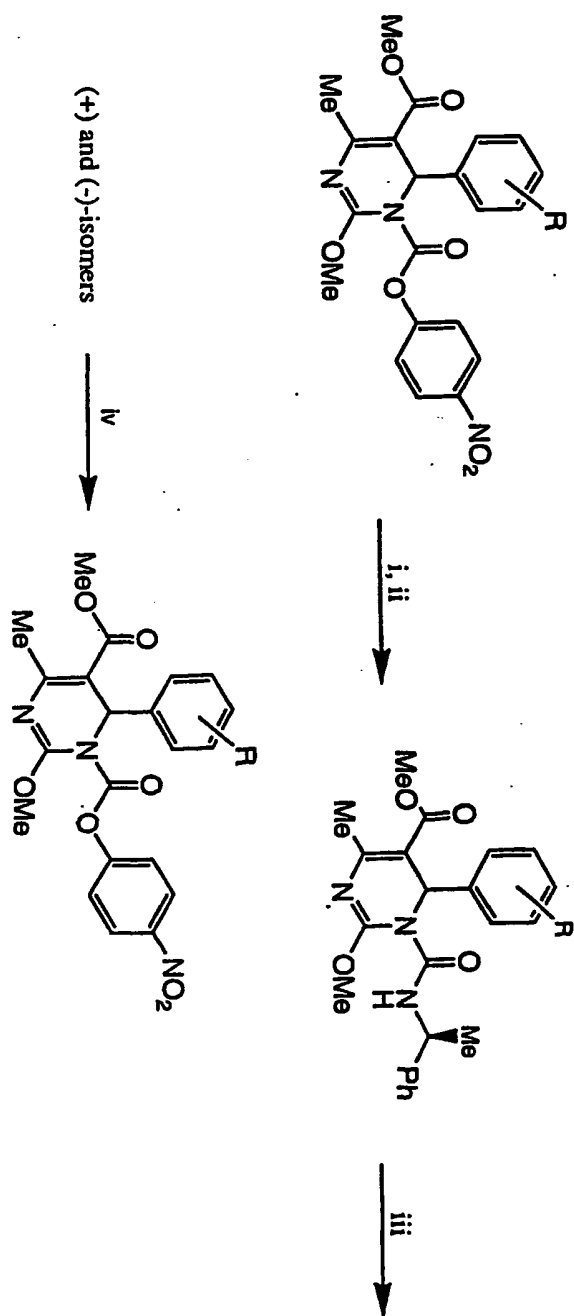
Scheme 5. Synthesis of dihydropyrimidinones



- i. O-Methylisourea, NaHCO_3 , DMF
- ii. $\text{NaOAc}/\text{NaHCO}_3$, DMF
- iii. 4-Nitrophenyl chloroformate, DMAP, CH_2Cl_2
- iv. Amine
- v. HCl/THF

-203-

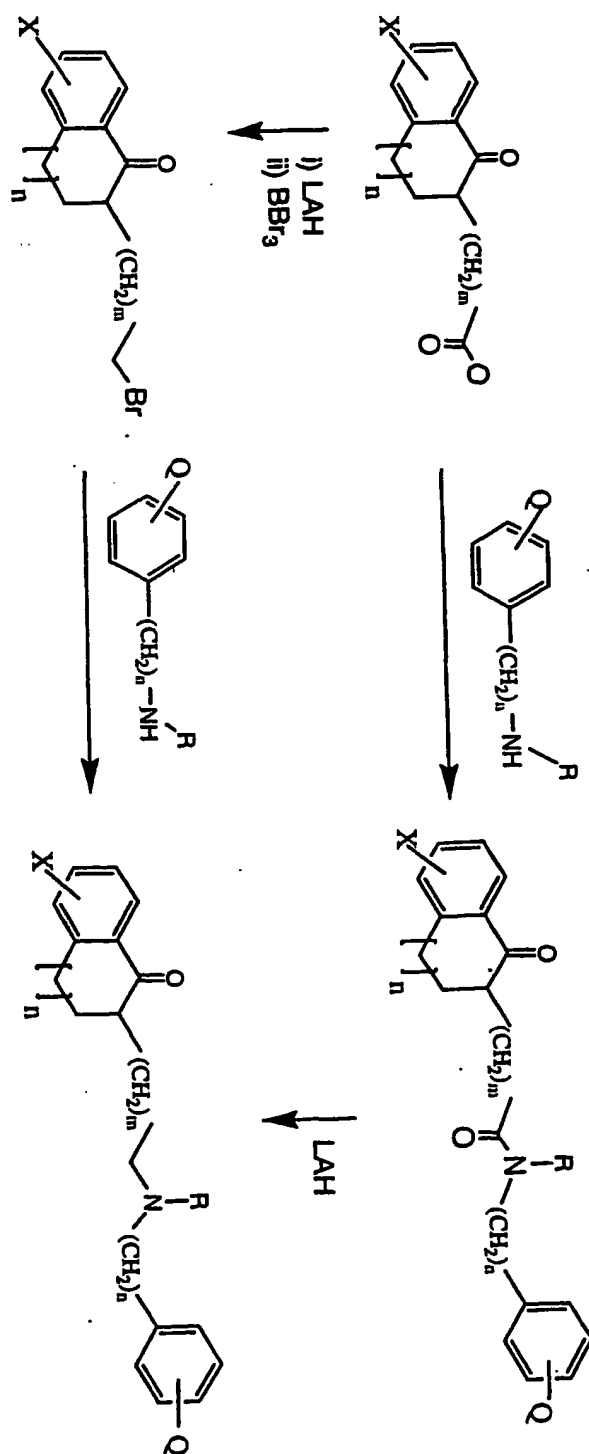
Scheme 6. Resolution of dihydropyrimidinones.



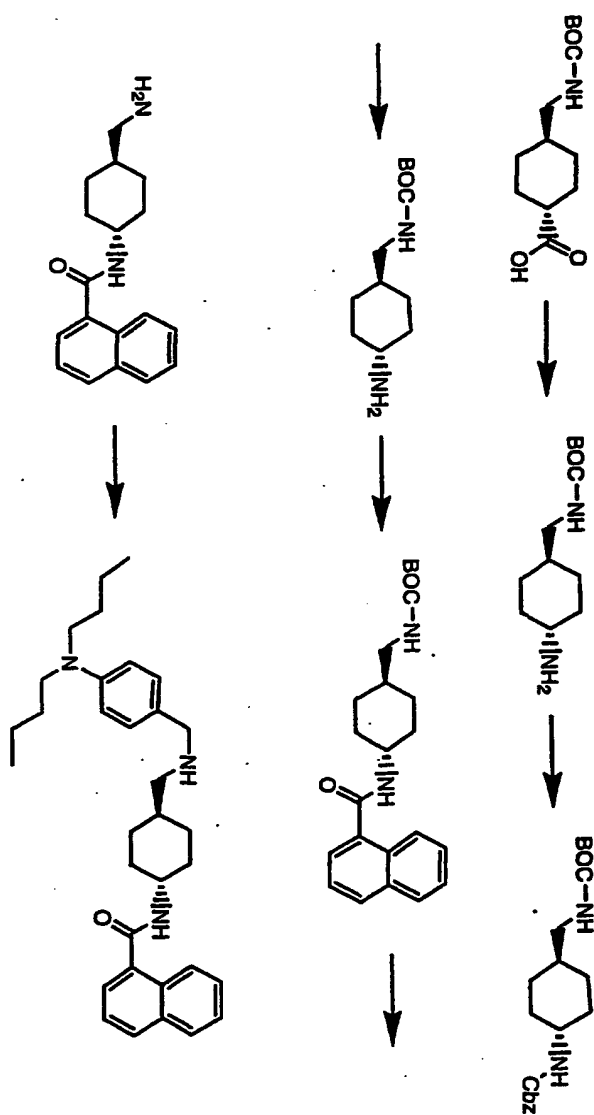
- i. S-(-)- α -Methylbenzylamine
- ii. Sepn. of diastereomers
- iii. DBU
- iv. p-nitrophenylchloroformate

-204-

Scheme 7. Synthesis of Example 5 and Analogs

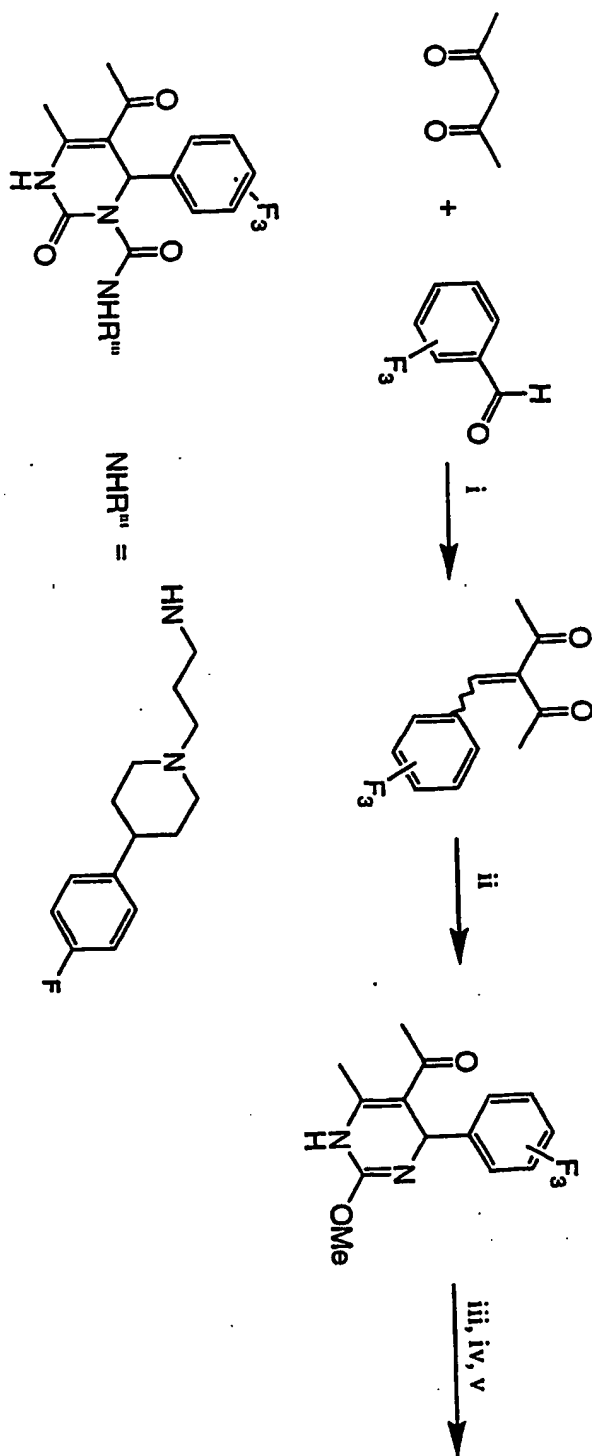


Scheme 8. Synthesis of Example 13

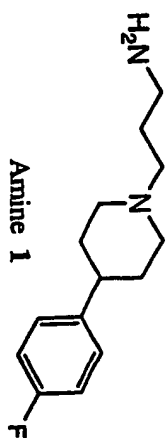


-206-

Scheme 9. Synthesis of Example 12

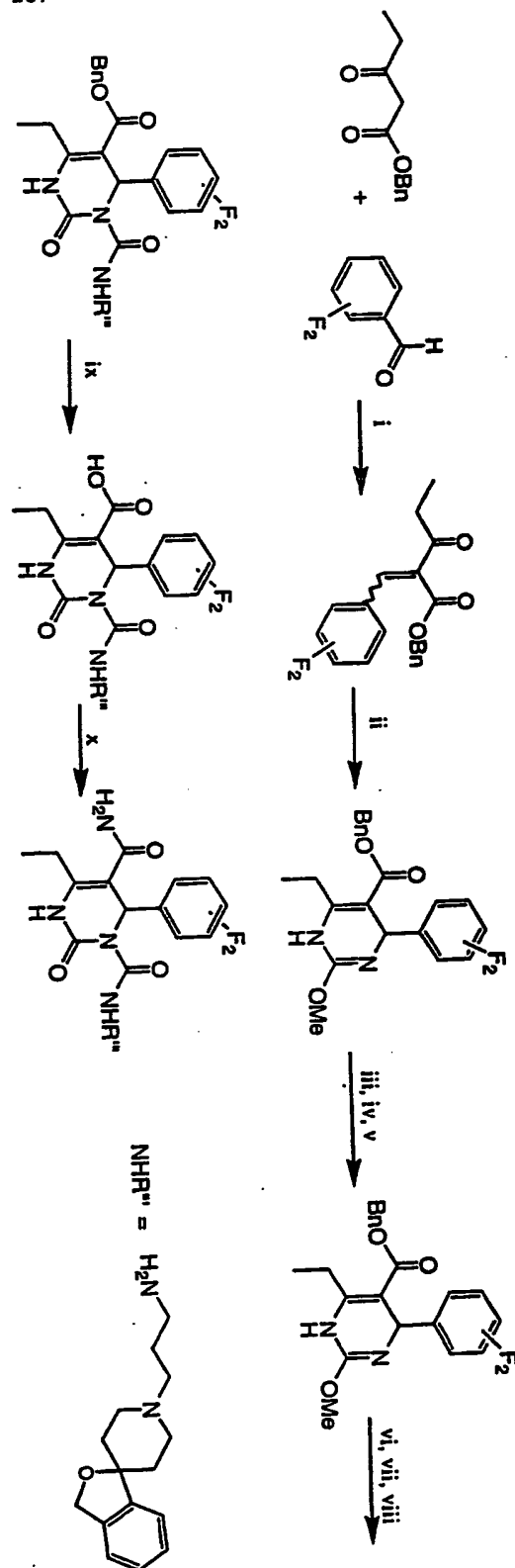


- i. Piperidine, Benzene
- ii. O-Methylisourea, NaHCO_3 , DMF
- iii. 4-Nitrophenyl chloroformate, Pyridine, CH_2Cl_2
- iv. Amine 1
- v. 6 N HCl

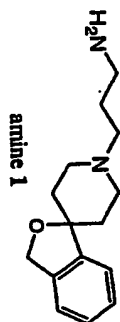


Scheme 10. Synthesis of Examples 4 and 22.

-207-

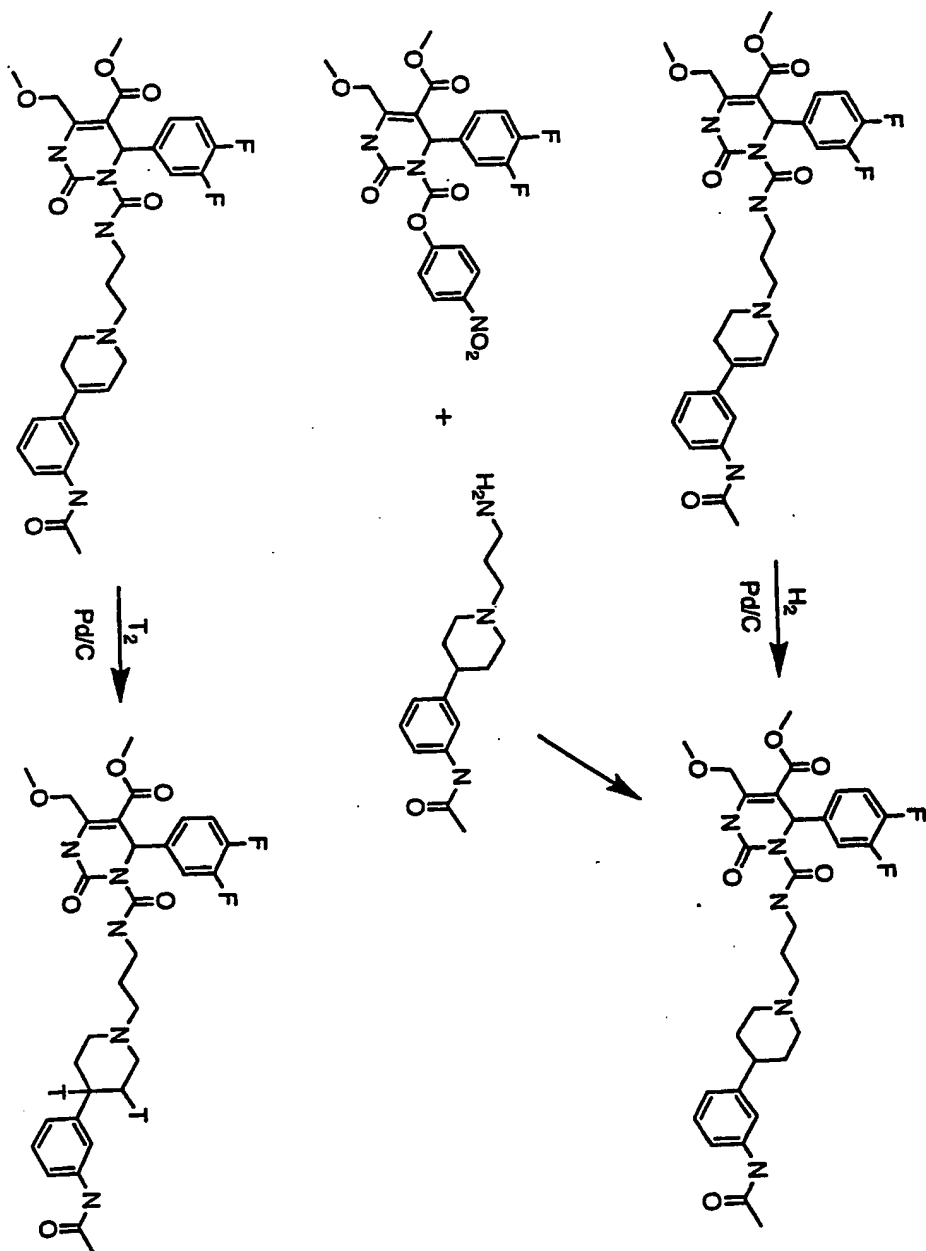


- i. Piperidine, Benzene
- ii. O-Methylisourea, NaHCO_3 , DMF
- iii. 4-Nitrophenyl chloroformate, Pyridine, CH_2Cl_2
- iv. R-(+)-Phenethylamine and separate diastereomers
- v. DBU
- vi. 4-Nitrophenyl chloroformate, Pyridine, CH_2Cl_2
- vii. Amine 1
- ix. 6 N HCl
- x. H_2 , Pd-C, MeOH/water
- x. EDC, NMM, NH_4OH , CH_2Cl_2

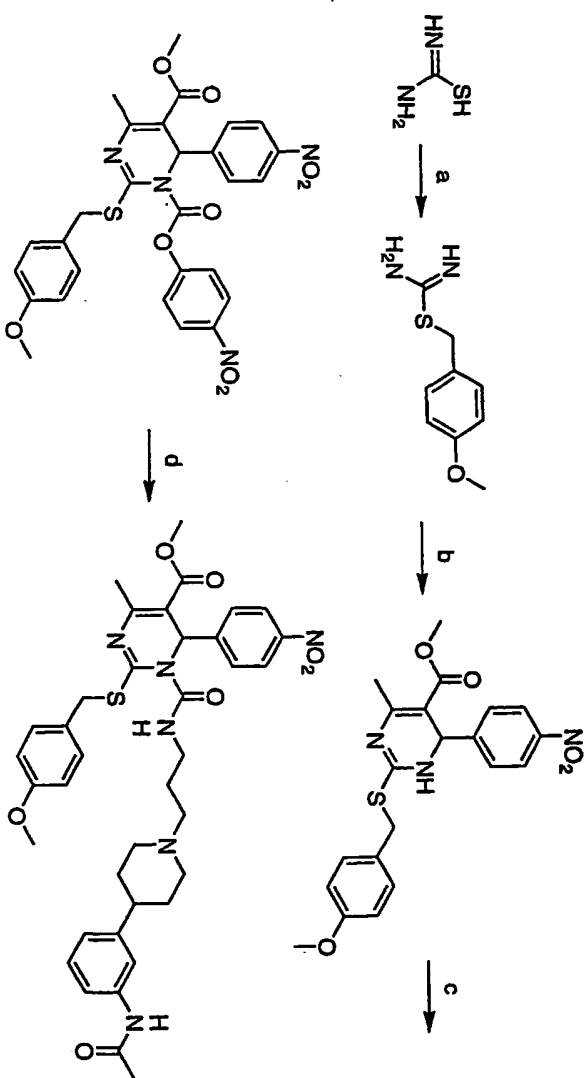


-208-

Scheme 11. Synthesis of Example 10 and its Tritiated Analog



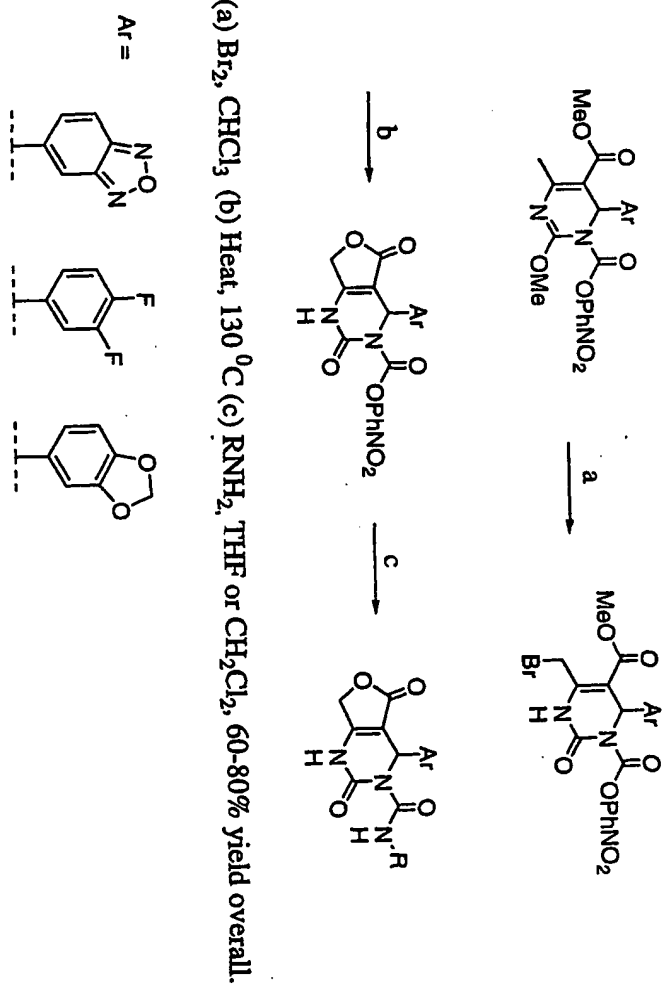
Scheme 12: Synthesis of Dihydropyrimidines



- a. p-methoxybenzyl chloride, THF, 0 to 65 °C;
b. Methyl 2-((4-nitrophenyl)methylene)-3-oxobutylate (prepared from p-nitrobenzaldehyde, methyl acetate, piperidinium acetate in isopropanol), NaOAc, DMF, 65 °C;
c. p-nitrophenyl chloroformate, NaHCO₃, dichloromethane
d. N'-(3-[1-(3-aminopropyl)-4-piperidinyl]phenyl)acetamide

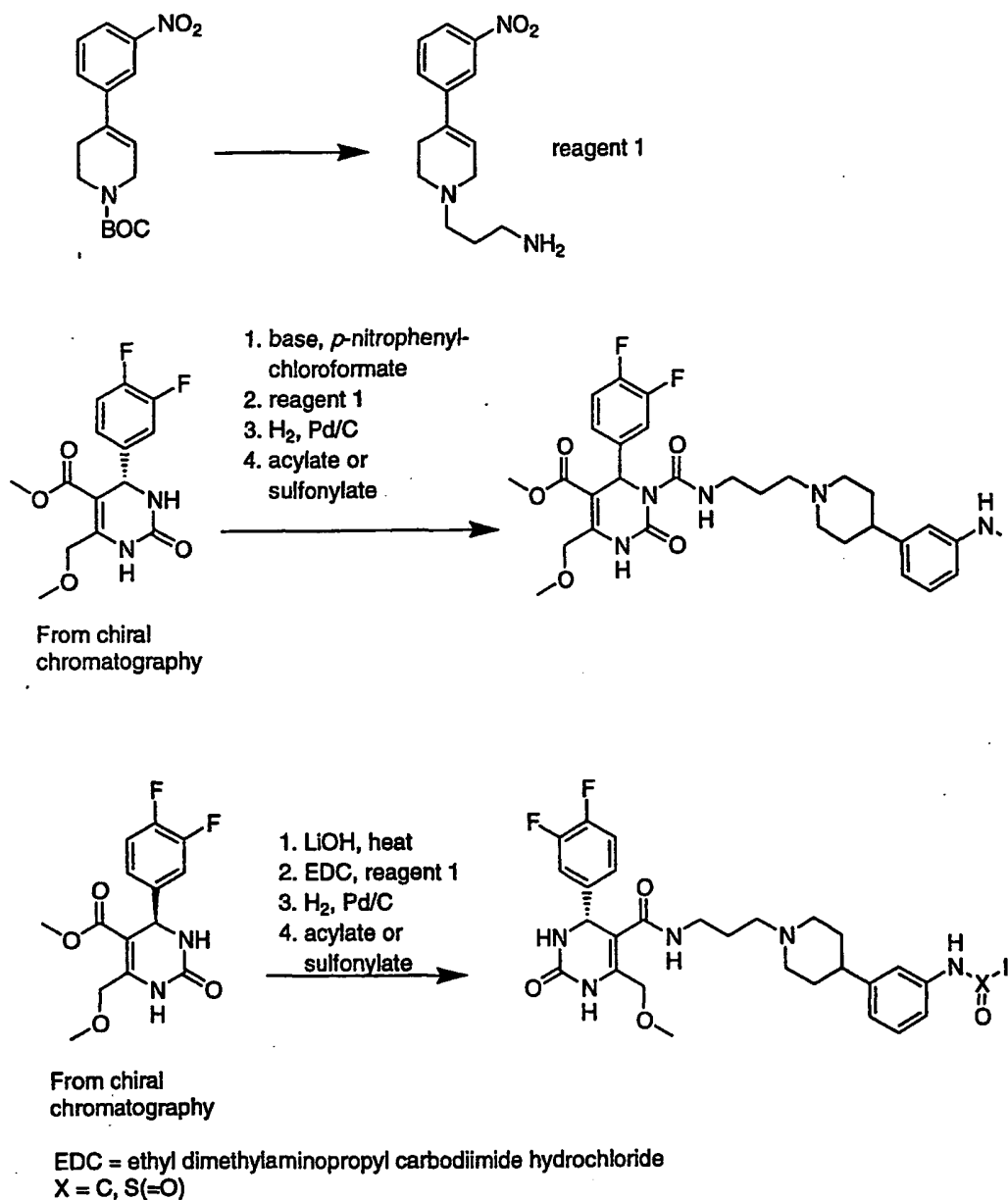
-210-

Scheme 13. Synthesis of Dihydropyrimidinone Fused Lactones



-211-

Scheme 14: Synthesis of Substituted Dihydropyrimidinones and Reverse Dihydropyrimidinones



-212-

II. Synthetic Methods for General Structures

The examples described in Section I are merely illustrative of the methods used to synthesize MCH1 antagonists. Further derivatives may be obtained utilizing generalized methods based on the synthetic methods used to synthesize the examples.

It may be necessary to incorporate protection and deprotection strategies for substituents such as amino, amido, carboxylic acid, and hydroxyl groups in the generalized synthetic methods to form further derivatives. Methods for protection and deprotection of such groups are well-known in the art, and may be found, for example in Green, T.W. and Wuts, P.G.M. (1991) Protection Groups in Organic Synthesis, 2nd Edition John Wiley & Sons, New York.

III. Oral Compositions

As a specific embodiment of an oral composition of a compound of this invention, 100 mg of one of the compounds described herein is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size 0 hard gel capsule.

IV. Pharmacological Evaluation of Compounds at Cloned MCH1, NPY, Galanin, and 5-HT2C Receptors

The pharmacological properties of the compounds of the present invention were evaluated at one or more of the cloned human MCH1, NPY1, NPY5, GALR1, GALR2, and GALR3 and rat 5-HT2C receptors using protocols described below.

Host cells

A broad variety of host cells can be used to study heterologously expressed proteins. These cells include but

-213-

are not restricted to assorted mammalian lines such as; Cos-7, CHO, LM(tk-), HEK293, etc.; insect cell lines such as; Sf9, Sf21, etc.; amphibian cells such as xenopus oocytes; and others.

5

COS-7 cells are grown on 150 mm plates in DMEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of COS-7 cells are trypsinized and split 1:6 every 3-4 days.

15

Human embryonic kidney 293 cells are grown on 150 mm plates in DMEM with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of 293 cells are trypsinized and split 1:6 every 3-4 days.

20

Mouse fibroblast LM(tk-) cells are grown on 150 mm plates in D-MEM with supplements (Dulbecco's Modified Eagle Medium with 10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of LM(tk-) cells are trypsinized and split 1:10 every 3-4 days.

25

Chinese hamster ovary (CHO) cells were grown on 150 mm plates in HAM's F-12 medium with supplements (10% bovine calf serum, 4 mM L-glutamine and 100 units/ml penicillin/100 µg/ml streptomycin) at 37°C, 5% CO₂. Stock plates of CHO cells are trypsinized and split 1:8 every 3-4 days.

30

Mouse embryonic fibroblast NIH-3T3 cells are grown on 150 mm plates in Dulbecco's Modified Eagle Medium (DMEM) with supplements (10% bovine calf serum, 4 mM glutamine, 100 units/ml penicillin/100 µg/ml streptomycin) at 37°C, 5% CO₂.

35

-214-

Stock plates of NIH-3T3 cells are trypsinized and split 1:15 every 3-4 days.

5 Sf9 and Sf21 cells are grown in monolayers on 150 mm tissue culture dishes in TMN-FH media supplemented with 10% fetal calf serum, at 27°C, no CO₂. High Five insect cells are grown on 150 mm tissue culture dishes in Ex-Cell 400™ medium supplemented with L-Glutamine, also at 27°C, no CO₂.

10 In some cases, cell lines that grow as adherent monolayers can be converted to suspension culture to increase cell yield and provide large batches of uniform assay material for routine receptor screening projects.

15 Transient expression

DNA encoding proteins to be studied can be transiently expressed in a variety of mammalian, insect, amphibian and other cell lines by several methods including but not restricted to; calcium phosphate-mediated, DEAE-dextran mediated, Liposomal-mediated, viral-mediated, electroporation-mediated and microinjection delivery. Each of these methods may require optimization of assorted experimental parameters depending on the DNA, cell line, and the type of assay to be subsequently employed.

25 A typical protocol for the calcium phosphate method as applied to LM(tk-) cells is described as follows; Adherent cells are harvested approximately twenty-four hours before transfection and replated at a density of $1-2 \times 10^5$ cells/cm² in a 100 mm tissue culture dish and allowed to incubate over night at 37°C at 5% CO₂. 250 µl of a mixture of CaCl₂ and DNA (20 µg DNA in 250 mM CaCl₂) is added to a 5 ml plastic tube and 250 µl of 2X HBS (250 mM NaCl, 10 mM KCl, 1.5 mM Na₂HPO₄, 12 mM dextrose, 50 mM HEPES) is slowly added with gentle mixing. The mixture is allowed to

30

35

-215-

incubate for 20 minutes at room temperature to allow a DNA precipitate to form. The cells are then washed with complete medium, 10 ml of culture medium is added to each plate, followed by addition of the DNA precipitate. The
5 cells are then incubated for 24 to 48 hours at 37°C at 5% CO₂.

A typical protocol for the DEAE-dextran method as applied to Cos-7 cells is described as follows; Cells to be used
10 for transfection are split 24 hours prior to the transfection to provide flasks which are 70-80% confluent at the time of transfection. Briefly, 8 µg of receptor DNA plus 8 µg of any additional DNA needed (e.g. G_α protein expression vector, reporter construct, antibiotic
15 resistance marker, mock vector, etc.) are added to 9 ml of complete DMEM plus DEAE-dextran mixture (10 mg/ml in PBS). Cos-7 cells plated into a T225 flask (sub-confluent) are washed once with PBS and the DNA mixture is added to each flask. The cells are allowed to incubate for 30 minutes at
20 37°C, 5% CO₂. Following the incubation, 36 ml of complete DMEM with 80 µM chloroquine is added to each flask and allowed to incubate an additional 3 hours. The medium is then aspirated and 24 ml of complete medium containing 10% DMSO for exactly 2 minutes and then aspirated. The cells
25 are then washed 2 times with PBS and 30 ml of complete DMEM added to each flask. The cells are then allowed to incubate over night. The next day the cells are harvested by trypsinization and reseeded as needed depending upon the type of assay to be performed.

30

A typical protocol for liposomal-mediated transfection as applied to CHO cells is described as follows; Cells to be used for transfection are split 24 hours prior to the transfection to provide flasks which are 70-80% confluent
35 at the time of transfection. A total of 10µg of DNA which

-216-

may include varying ratios of receptor DNA plus any additional DNA needed (e.g. G_{α} protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) is used to transfect each 75 cm² flask of cells. Liposomal mediated transfection is carried out according to the manufacturer's recommendations (LipofectAMINE, GibcoBRL, Bethesda, MD). Transfected cells are harvested 24 h post transfection and used or reseeded according the requirements of the assay to be employed.

10

A typical protocol for the electroporation method as applied to Cos-7 cells is described as follows; Cells to be used for transfection are split 24 hours prior to the transfection to provide flasks which are subconfluent at the time of transfection. The cells are harvested by trypsinization resuspended in their growth media and counted. 4×10^6 cells are suspended in 300 μ l of DMEM and placed into an electroporation cuvette. 8 μ g of receptor DNA plus 8 μ g of any additional DNA needed (e.g. G_{α} protein expression vector, reporter construct, antibiotic resistance marker, mock vector, etc.) is added to the cell suspension, the cuvette is placed into a BioRad Gene Pulser and subjected to an electrical pulse (Gene Pulser settings: 0.25 kV voltage, 950 μ F capacitance). Following the pulse, 800 μ l of complete DMEM is added to each cuvette and the suspension transferred to a sterile tube. Complete medium is added to each tube to bring the final cell concentration to 1×10^5 cells/100 μ l. The cells are then plated as needed depending upon the type of assay to be performed.

30

A typical protocol for viral mediated expression of heterologous proteins is described as follows for baculovirus infection of insect Sf9 cells. The coding region of DNA encoding the receptor disclosed herein may be subcloned into pBlueBacIII into existing restriction sites

35

-217-

or sites engineered into sequences 5' and 3' to the coding region of the polypeptides. To generate baculovirus, 0.5 µg of viral DNA (BaculoGold) and 3 µg of DNA construct encoding a polypeptide may be co-transfected into 2 x 10⁶ *Spodoptera frugiperda* insect Sf9 cells by the calcium phosphate co-precipitation method, as outlined in by Pharmingen (in "Baculovirus Expression Vector System: Procedures and Methods Manual"). The cells then are incubated for 5 days at 27°C. The supernatant of the co-transfection plate may be collected by centrifugation and the recombinant virus plaque purified. The procedure to infect cells with virus, to prepare stocks of virus and to titer the virus stocks are as described in Pharmingen's manual. Similar principals would in general apply to mammalian cell expression via retro-viruses, Simliki forest virus and double stranded DNA viruses such as adeno-, herpes-, and vacinia-viruses, and the like.

Stable expression

Heterologous DNA can be stably incorporated into host cells, causing the cell to perpetually express a foreign protein. Methods for the delivery of the DNA into the cell are similar to those described above for transient expression but require the co-transfection of an ancillary gene to confer drug resistance on the targeted host cell. The ensuing drug resistance can be exploited to select and maintain cells that have taken up the heterologous DNA. An assortment of resistance genes are available including but not restricted to Neomycin, Kanamycin, and Hygromycin. For the purposes of receptor studies, stable expression of a heterologous receptor protein is carried out in, but not necessarily restricted to, mammalian cells including, CHO, HEK293, LM(tk-), etc.

-218-

Cell membrane preparation

For binding assays, pellets of transfected cells are suspended in ice-cold buffer (20 mM Tris.HCl, 5 mM EDTA, pH 7.4) and homogenized by sonication for 7 sec. The cell lysates are centrifuged at 200 x g for 5 min at 4°C. The supernatants are then centrifuged at 40,000 x g for 20 min at 4°C. The resulting pellets are washed once in the homogenization buffer and suspended in binding buffer (see methods for radioligand binding). Protein concentrations are determined by the method of Bradford (1976) using bovine serum albumin as the standard. Binding assays are usually performed immediately, however it is possible to prepare membranes in batch and store frozen in liquid nitrogen for future use.

Radioligand binding assays

Radioligand binding assays for the MCH1 receptor were carried out using plasmid pEXJ.HR-TL231 (ATCC Accession No. 203197). Plasmid pEXJ.HR-TL231 comprises the regulatory elements necessary for expression of DNA in a mammalian cell operatively linked to DNA encoding the human MCH1 receptor so as to permit expression thereof. Plasmid pEXJ.HR-TL231 was deposited on September 17, 1998, with the American Type Culture Collection (ATCC), 12301 Parklawn Drive, Rockville, Maryland 20852, U.S.A. under the provisions of the Budapest Treaty for the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure and was accorded ATCC Accession No. 203197.

Human embryonic kidney 293 cells (A293 cells) were stably transfected with DNA encoding the MCH1 receptor utilizing the calcium phosphate method and cell membranes were prepared as described above. Binding experiments with membranes from A293 cells transfected with the human MCH1

-219-

receptor were performed with 0.08 nM [³H]Compound 10 (custom labeled by Amersham) using an incubation buffer consisting of 50 mM Tris pH 7.4, 10 mM MgCl₂, 0.16 mM PMSF, 1 mM 1,10 phenantroline and 0.2% BSA. Binding was performed at 25°C for 90 minutes. Incubations were terminated by rapid vacuum filtration over GF/C glass fiber filters, presoaked in 5% PEI using 50 mM Tris pH 7.4 as wash buffer. In all experiments, nonspecific binding is defined using 10 μM Compound 10.

The methods to obtain the cDNA of the human NPY1, NPY5, GALR1, GALR2, and GALR3 and rat 5-HT_{2C} receptors, express said receptors in heterologous systems, and carry out assays to determine binding affinity are described in the following publications and above: human NPY1 (Larhammar et al., 1992), human NPY5 (U.S. Patent No. 5,602,024, the disclosure of which is hereby incorporated by reference in its entirety into this application), human Gal1 (Habert-Ortoli et al., 1994), human Gal2 (Smith et al., 1997), human Gal3 (Smith et al., 1998), and rat 5-HT_{2C} (Julius et al., 1988).

Functional assays

Cells may be screened for the presence of endogenous mammalian receptor using functional assays (described in detail below). Cells with no or a low level of endogenous receptor present may be transfected with the exogenous receptor for use in the following functional assays.

A wide spectrum of assays can be employed to screen for receptor activation. These range from traditional measurements of phosphatidyl inositol, cAMP, Ca⁺⁺, and K⁺, for example; to systems measuring these same second messengers but which have been modified or adapted to be higher throughput, more generic, and more sensitive; to

-220-

cell based platforms reporting more general cellular events resulting from receptor activation such as metabolic changes, differentiation, and cell division/proliferation, for example; to high level organism assays which monitor complex physiological or behavioral changes thought to be involved with receptor activation including cardiovascular, analgesic, orexigenic, anxiolytic, and sedation effects, for example.

10 Functional assay:

Intracellular calcium mobilization assay

Intracellular calcium mobilization assays for the MCH1 receptor were carried out using plasmid pEXJ.HR-TL231 (ATCC Accession No. 203197). COS-7 cells were transiently transfected with DNA encoding the MCH1 receptor utilizing the DEAE-dextran method as described above. The intracellular free calcium concentration was measured by fluorescent imaging using the calcium sensitive fluorescent dye Fluo-3. COS-7 cells expressing the human MCH1 receptor were seeded onto sterile 96 well plates, washed with Hank's balanced salt solution (HBSS), containing 20 mM HEPES, 2.5 mM probenecid, and 0.1% BSA, and loaded with the same buffer containing 3.8 μ M Fluo-3 for 1 hour at 37°C. After washing with HBSS to remove the fluo-3 solution, cells were equilibrated for 10 minutes. Cells were then incubated with, or without MCH, and the fluorescence is measured using a Fluorescence Imaging Plate Reader (FLIPR, Molecular Devices).

30 Materials

Cell culture media and supplements were from Specialty Media (Lavallette, NJ). Cell culture plates (150 mm and 96-well microtiter) were from Corning (Corning, NY). Sf9, Sf21, and High Five insect cells, as well as the baculovirus transfer plasmid, pBlueBacIII™, were purchased

-221-

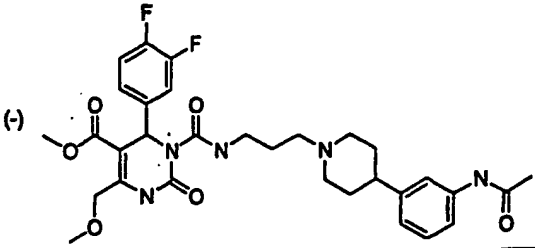
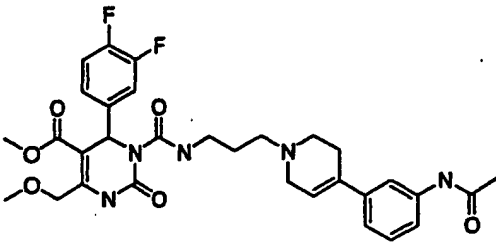
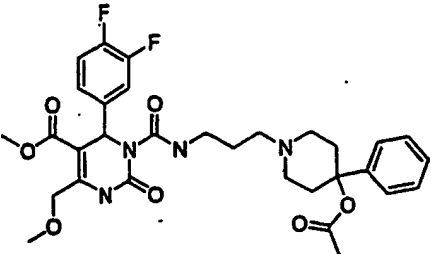
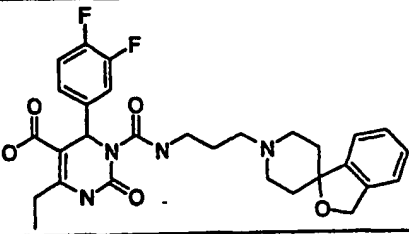
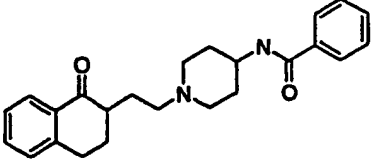
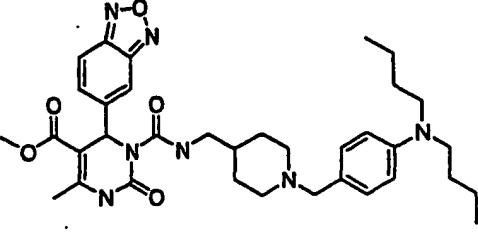
from Invitrogen (San Diego, CA). TMN-FH insect medium complemented with 10% fetal calf serum, and the baculovirus DNA, BaculoGold™, was obtained from Pharmingen (San Diego, CA.). Ex-Cell 400™ medium with L-Glutamine was purchased
5 from JRH Scientific. Polypropylene 96-well microtiter plates were from Co-star (Cambridge, MA). Commercially available MCH and related peptide analogs were either from Bachem California (Torrance, CA) or Peninsula (Belmont, CA). Bio-Rad Reagent was from Bio-Rad (Hercules, CA).
10 Bovine serum albumin (ultra-fat free, A-7511) was from Sigma (St. Louis. MO). All other materials were reagent grade.

Functional Assay Results

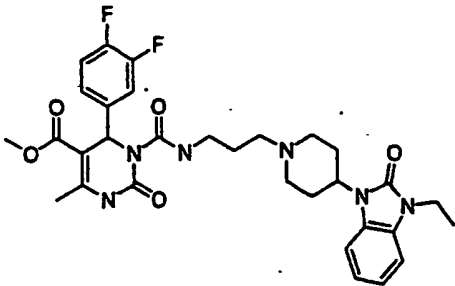
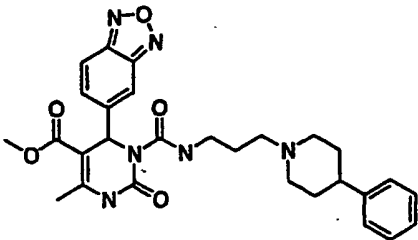
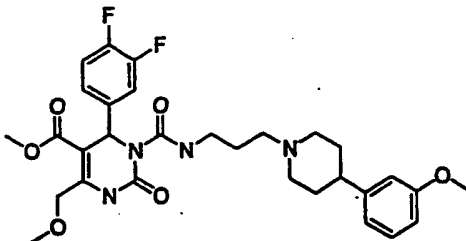
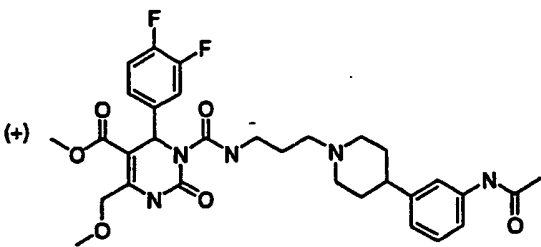
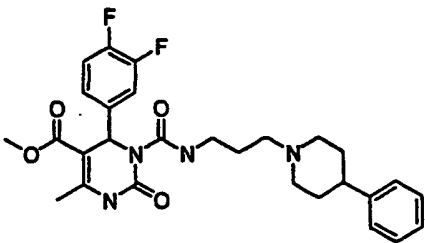
15 The compounds of Examples 1-37 were assayed using the cloned human MCH1 receptor. The preferred compounds were found to be selective MCH1 antagonists. The results are summarized in Table 1.

20

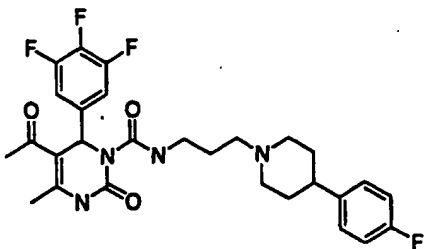
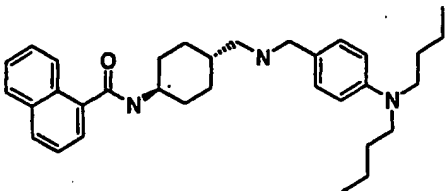
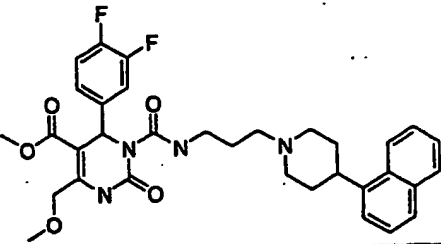
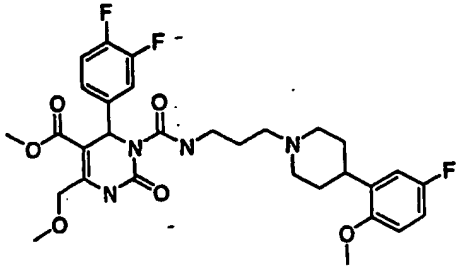
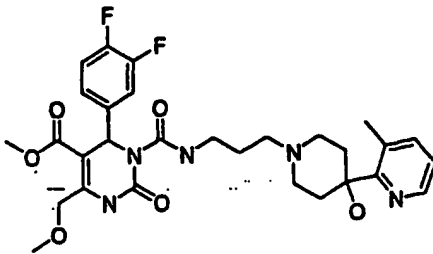
Table 1

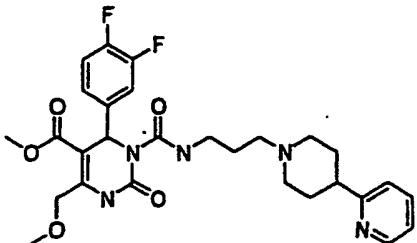
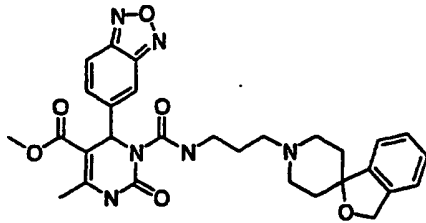
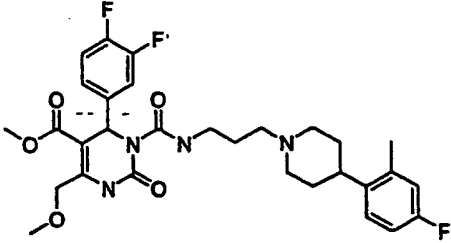
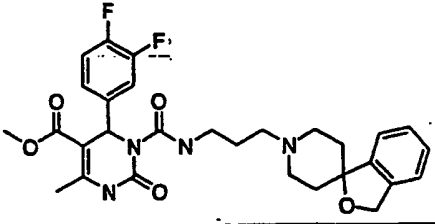
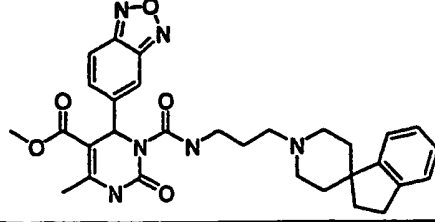
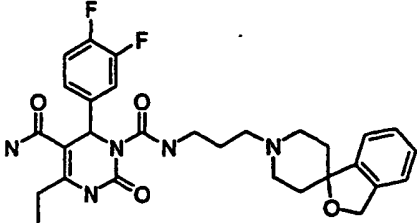
EXAMPLE No.	STRUCTURE	Kb (nM) hMCH1
1		42
2		18
3		201
4		187
5		258
6		42

-223-

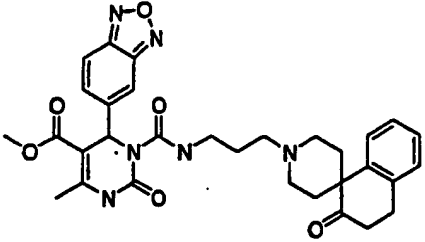
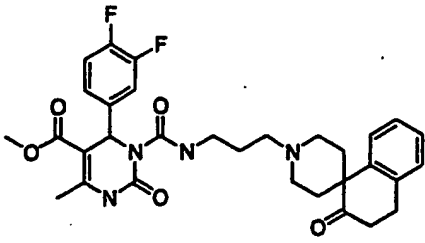
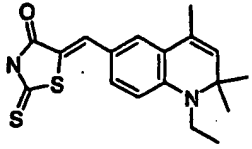
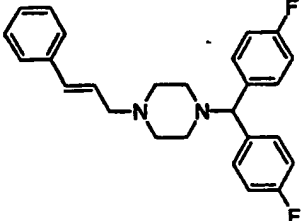
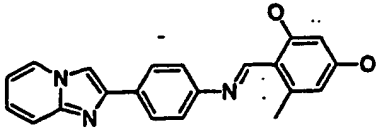
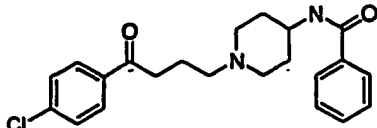
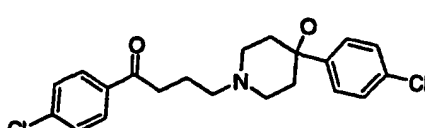
EXAMPLE No.	STRUCTURE	Kb (nM) hMCH1
7		41
8		88
9		35
10		0.3
11		331

-224-

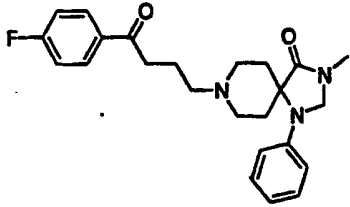
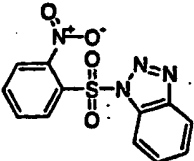
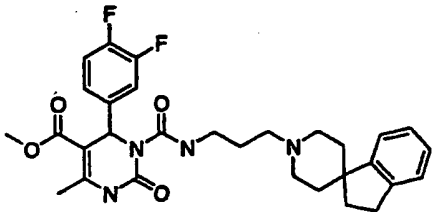
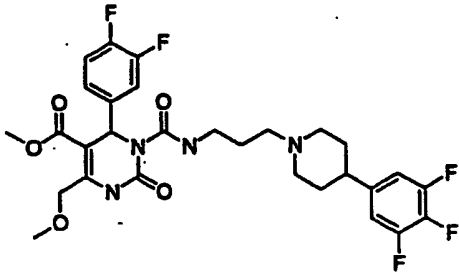
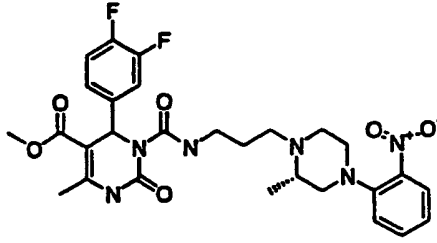
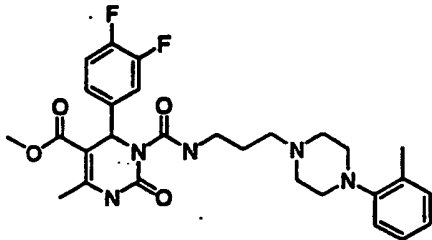
EXAMPLE No.	STRUCTURE	K _b (nM) hMCH1
12		29
13		284
14		2
15		289
16		329

EXAMPLE No.	STRUCTURE	K _b (nM) hMCH1
17		373
18		1
19		7
20		5
21		28
22		40

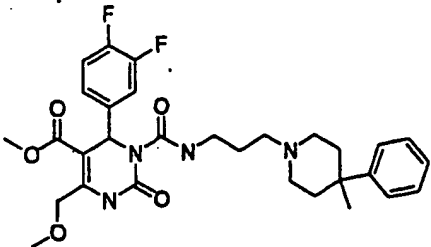
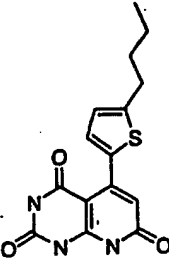
-226-

EXAMPLE No.	STRUCTURE	Kb (nM) hMCH1
23		68
24		102
25		126
26		260
27		279
28		60
29		9

-227-

EXAMPLE No.	STRUCTURE	K _b (nM) hMCH1
30		479
31		7
32		67
33		12
34		182
35		276

-228-

EXAMPLE No.	STRUCTURE	K _b (nM) hMCH1
36		406
37		162

-229-

Radioligand Binding Assay Results

5 The compounds of Examples 1 to 37 were assayed using cloned human MCH1, NPY1, NPY5, GALR1, GALR2, and GALR3 and rat 5-HT2C receptors. The binding affinities of several compounds are shown in Tables 2 and 3.

The compounds of Examples 38 to 56 were assayed using the cloned rat MCH1 receptor. The binding affinities (K_i) of these compounds are shown in Table 4.

Table 2: Antagonist potency (Kb) at the human MCH1 receptor, and binding affinity (Ki) at NPY, galanin and 5HT2C receptors.

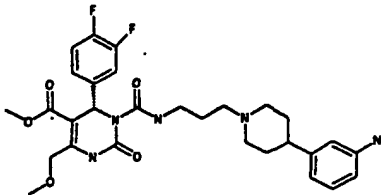
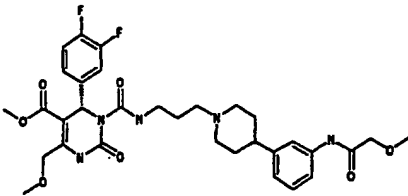
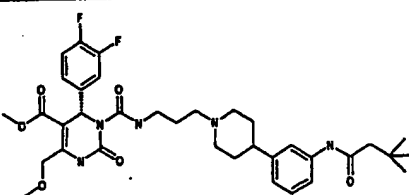
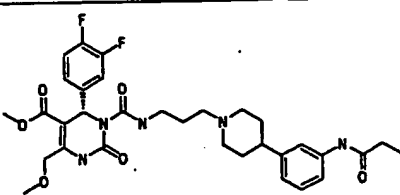
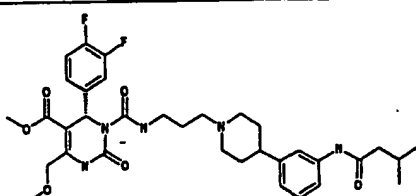
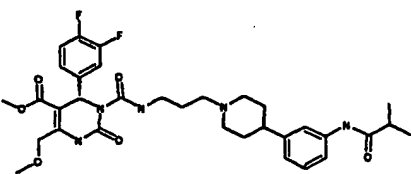
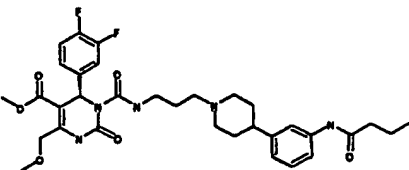
Compound	hMCH1 Kb (nM)	hNPY1 Ki (nM)	hNPY5 Ki (nM)	hGALR1 Ki (nM)	hGALR2 Ki (nM)	hGALR3 Ki (nM)	5HT2C Ki (nM)
10	0.3	>50000	>50000	>50000	>50000	>50000	29,585
18	1	>50000	>50000	>50000	>50000	>50000	32,617
14	2	ND	ND	>50000	42,603	>50000	663
20	5	27,076	>50000	>50000	>50000	>50000	15,058
19	7	>50000	>50000	>50000	>50000	>50000	11,720
29	9	>50000	46,075	>50000	>50000	>50000	>50000
2	18	ND	ND	>50000	>50000	>50000	39,837
6	42	6,667	4,735	11,057	14,921	21,095	25,549
1	42	>50000	>50000	>50000	>50000	>50000	>50000
28	60	>50000	>50000	>50000	>50000	>50000	34,087
25	126	>50000	>50000	>50000	>50000	>50000	41,009
37	162	>50000	>50000	>50000	>50000	>50000	>50000
4	187	>50000	>50000	>50000	>50000	>50000	34,798
26	260	>50000	>50000	>50000	>50000	>50000	2,900
27	279	>50000	>50000	>50000	>50000	>50000	>50000
13	284	9,601	>50000	11,262	4,727	5,985	25,030
30	479	>50000	>50000	>50000	>50000	>50000	8,859

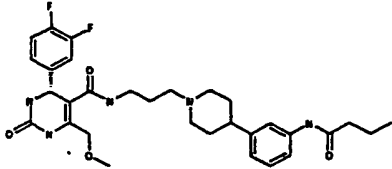
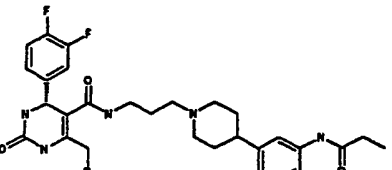
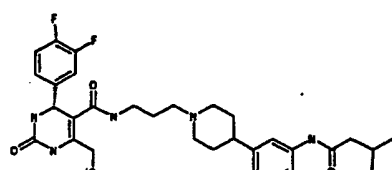
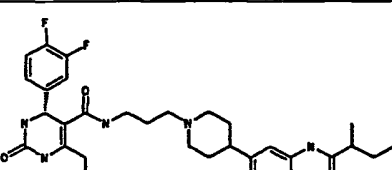
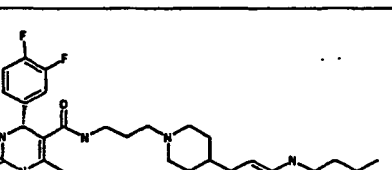
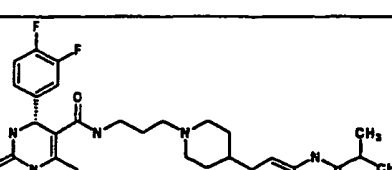
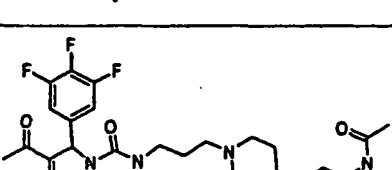
Table 3: Antagonist potency (Kb) at the human MCH1 receptor, and binding affinity (Ki) at human MCH1, NPY1, NPY5, GALR1, GALR2, GALR3, and rat 5HT2C receptors.

Compound	hMCH1	hMCH1 *	hNPY1	hNPY5	hGALR1	hGALR2	hGALR3	r5HT2C
	Kb (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)	Ki (nM)
10	0.3	0.08	>50000	>50000	>50000	>50000	>50000	29,585
19	7	3	>50000	>50000	>50000	>50000	>50000	11,720
18	1	4	>50000	>50000	>50000	>50000	>50000	32,617
20	5	6	27,076	>50000	>50000	>50000	>50000	15,058
1	42	40	>50000	>50000	>50000	>50000	>50000	>50000
2	18	49	ND	ND	>50000	>50000	>50000	39,837
14	2	50	ND	ND	>50000	42,603	>50000	663
4	187	131	>50000	>50000	>50000	>50000	>50000	34,798
13	284	171	9,601	>50000	11,262	4,727	5,985	25,030
29	9	350	>50000	46,075	>50000	>50000	>50000	>50000
6	42	463	6,667	4,735	11,057	14,921	21,095	25,549

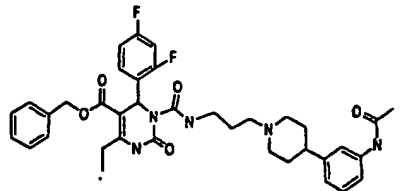
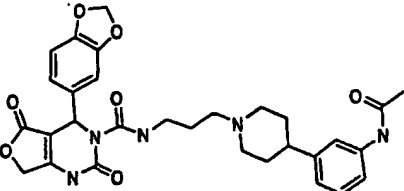
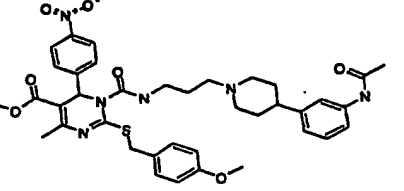
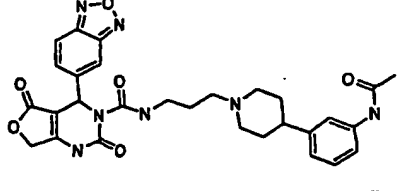
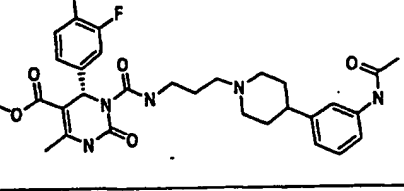
* Binding affinity (Ki) was determined in competition binding assays using membrane preparations of A293 cells expressing the human MCH1 receptor and [³H]Compound 10 as the radioligand.

Table 4

EXAMPLE No.	STRUCTURE	Ki (nM) rMCH1
38		1.34
39		3.33
40		2.72
41		0.04
42		0.6
43		0.23
44		0.09

45		14.69
46		8.16
47		34.28
48		22.15
49		225.47
50		13.74
51		0.79

-234-

52		0.81
53		50.76
54		29.87
55		203.74
56		0.26

REFERENCES

- 5 Auburger, G., et al., (1992) Assignment of the second (cuban) locus of autosomal dominant cerebellar ataxia to chromosome 12q23-24.1, between flanking markers D12S58 and PLA2. *Cytogenet. Cell. Genet.* 61:252-256.
- 10 Bahjaoui-Bouhaddi, M., et al., (1994) Insulin treatment stimulates the rat melanin-concentrating hormone-producing neurons. *Neuropeptides* 24:251-258.
- Baker, B.I. (1991) Melanin-concentrating hormone: a general vertebrate neuropeptide. *Int. Rev. Cytol.* 126:1-47.
- 15 Baker, B.I. (1994) Melanin-concentrating hormone update: functional consideration. *TEM* 5:120-126.
- Bassett, A.S., et al., (1988) Partial trisomy chromosome 5 cosegregating with schizophrenia. *Lancet* 1:799-801.
- 20 Bittencourt, J.C., et al., (1992) The melanin-concentrating hormone system of the rat brain: An immuno- and hybridization histochemical characterization. *J. Comp. Neurol.* 319:218-245.
- 25 Burgaud, J.L., et al., (1997) Melanin-concentrating hormone binding sites in human SVK14 keratinocytes. *Biochem.Biophys.Res.Comm.* 241(3):622-629.
- 30 Craddock, N., et al., (1993) The gene for Darier's disease maps to chromosome 12q23-q24.1. *Hum. Mol. Genet.* 2:1941-1943.
- Drozdz, R. and Eberle, A.N. (1995) Binding sites for

-236-

melanin-concentrating hormone (MCH) in brain synaptosomes and membranes from peripheral tissues identified with highly tritiated MCH. *J. Recept. Signal. Transduct. Res.* 15(1-4):487-502.

5

Drozdz, R., et al., (1995) Melanin-concentrating hormone binding to mouse melanoma cells in vitro. *FEBS* 359:199-202.

10

Drozdz, R., et al., (1998) Characterization of the receptor for melanin-concentrating hormone on melanoma cells by photocrosslinking. *Ann. NY Acad. Sci.* 839(1):210-213.

15

Gilliam, T.C., et al., (1989) Deletion mapping of DNA markers to a region of chromosome 5 that cosegregates with schizophrenia. *Genomics* 5:940-944.

20

Gonzalez, M.I., et al., (1997) Stimulatory effect of melanin-concentrating hormone on luteinizing hormone release. *Neuroendocrinology* 66(4):254-262.

25

Gonzalez, M.I., et al., (1997) α -melanocyte-stimulating hormone (α -MSH) and melanin-concentrating hormone (MCH) modify monoaminergic levels in the preoptic area of the rat. *Peptides* 18:387-392.

30

Gonzalez, M.I., et al., (1996) Behavioral effects of α -melanocyte-stimulating hormone (α -MSH) and melanin-concentrating hormone (MCH) after central administration in female rats. *Peptides* 17:171-177.

35

Grillon, S., et al., (1997) Exploring the expression of the melanin-concentrating hormone messenger RNA in the rat lateral hypothalamus after goldthioglucose injection. *Neuropeptides* 31(2):131-136.

-237-

- Habert-Ortoli, E., et al., (1994) Molecular cloning of a functional human galanin receptor. *Proc Natl Acad Sci USA* 91:9780-9783.
- 5 Herve, C. and Fellmann, D. (1997) Changes in rat melanin-concentrating hormone and dynorphin messenger ribonucleic acids induced by food deprivation. *Neuropeptides* 31(3):237-242.
- 10 Hervieu, G., et al., (1996) Development and stage-dependent expression of melanin-concentrating hormone in mammalian germ cells. *Biology of Reproduction* 54:1161-1172.
- 15 Julius, D., et al., (1988) Molecular characterization of a functional cDNA encoding the serotonin 1c receptor. *Science* 241:558-564.
- 20 Kawachi, H., et al., (1983) Characterization of melanin-concentrating hormone in chum salmon pituitaries. *Nature* 305:321-333.
- 25 Knigge, K.M., et al., (1996) Melanotropic peptides in the mammalian brain: The melanin-concentrating hormone. *Peptides* 17:1063-1073.
- 30 Knigge, K.M. and Wagner, J.E. (1997) Melanin-concentrating hormone (MCH) involvement in pentylentetrazole (PTZ)-induced seizure in rat and guinea pig. *Peptides* 18(7):1095-1097.
- 35 Larhammar, D., et al., (1992) Cloning and functional expression of a human neuropeptide Y/peptide YY receptor of the Y1 type. *J Biol Chem.* 267:10935-10938.
- Ludwig, D.S., et al., (1998) Melanin-concentrating hormone:

-238-

a functional melanocortin antagonist in the hypothalamus.
Am. J. Physiol. Endocrinol. Metab. 274(4):E627-E633.

5 MacKenzie, F.J., et al., (1984) Evidence that the
dopaminergic incerto-hypothalamic tract has a stimulatory
effect on ovulation and gonadotropin release.
Neuroendocrinology 39:289-295.

10 McBride, R.B., et al., (1994) The actions of melanin-
concentrating hormone (MCH) on passive avoidance in rats:
A preliminary study. *Peptides* 15:757-759.

15 Melki, J., et al., (1990) Gene for chronic proximal spinal
muscular atrophies maps to chromosome 5q. *Nature* (London)
344:767-768.

Miller, C.L., et al., (1993) α -MSH and MCH are functional
antagonists in a CNS auditory paradigm. *Peptides* 14:1-10.

20 Nahon, J.L., et al., (1989) The rat melanin-concentrating
hormone mRNA encodes multiple putative neuropeptides
coexpressed in the dorsolateral hypothalamus. *Endocrinology*
125:2056-2065.

25 Nahon, J-L. (1994) The melanin-concentrating hormone: from
the peptide to the gene. *Critical Rev. in Neurobiol*
221:221-262.

30 Parkes, D.G. (1996) Diuretic and natriuretic actions of
melanin concentrating hormone in conscious sheep. *J.*
Neuroendocrinol. 8:57-63.

35 Pedoutour, F., et al., (1994) Assignment of the human pro-
melanin-concentrating hormone gene (PMCH) to chromosome
12q23-24 and two variant genes (PMCHL1 and PMCHL2) to

-239-

chromosome 5p14 and 5q12-q13. *Genomics* 19:31-37.

Presse, F., et al. (1992) Rat melanin-concentrating hormone messenger ribonucleic acid expression: marked changes
5 during development and after stress and glucocorticoid stimuli. *Endocrinology* 131:1241-1250.

Qu, D., et al. (1996) A role for melanin-concentrating hormone in the central regulation of feeding behaviour.
10 *Nature* 380:243-247.

Rossi, M., et al., (1997) Melanin-concentrating hormone acutely stimulates feeding, but chronic administration has no effect on body weight. *Endocrinology* 138:351-355.

15 Sahu, A. (1998) Evidence suggesting that galanin (GAL), melanin-concentrating hormone (MCH), neurotensin (NT), proopiomelanocortin (POMC) and neuropeptide Y (NPY) are targets of leptin signaling in the hypothalamus.
20 *Endocrinology* 139(2):795-798.

Sakurai, T., et al., (1998) Orexins and orexin receptors: A family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*
25 92:573-585.

Sanchez, M., et al., (1997) Melanin-concentrating hormone (MCH) antagonizes the effects of α -MSH and neuropeptide E-I on grooming and locomotor activities in the rat. *Peptides*
30 18:393-396.

Sherrington, R., et al., (1988) Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature* (London) 336:164-167.

35

-240-

- Smith. K.E., et al., (1998) Cloned human and rat galanin GALR3 receptors. Pharmacology and activation of G-protein inwardly rectifying K⁺ channels. *J Biol Chem* 273:23321-23326.
- 5 Smith, K.E., et al. (1997) Expression cloning of a rat hypothalamic galanin receptor coupled to phosphoinositide turnover. *J Biol Chem* 272:24612-24616.
- 10 Twells, R., et al., (1992) Chromosomal assignment of the locus causing olivo-ponto-cerebellar atrophy (SCA2) in a cuban founder population. *Cytogenet. Cell. Genet.* 61:262-265.
- 15 Westbrook, C.A., et al., (1992) Report of the second international workshop on human chromosome 5 mapping. *Cytogenet. Cell. Genet.* 61:225-231.

-241-

What is claimed is:

1. A compound having the structure:

5

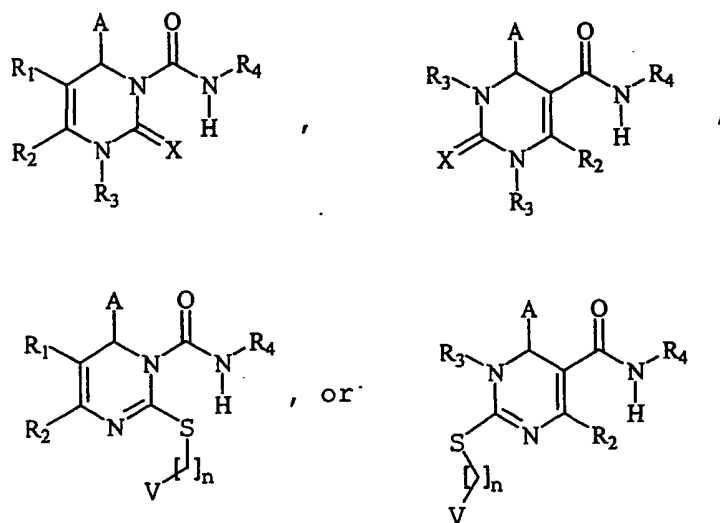
10

15

20

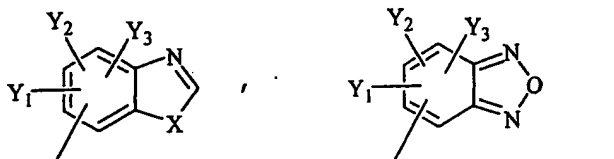
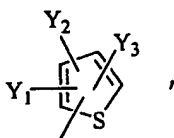
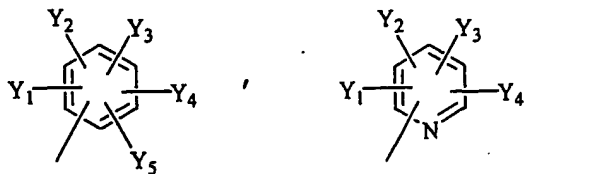
25

30

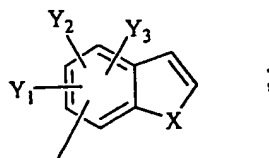


-242-

wherein A is



or



25

wherein each of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 is independently -H; straight chained or branched C_1 - C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2 - C_7 alkenyl or alkynyl; C_3 - C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; - NO_2 ; - N_3 ; -CN; - OR_3 , - $OCOR_3$, - COR_3 , - $CON(R_3)_2$, or - $COOR_3$; or any two of Y_1 , Y_2 , Y_3 , Y_4 and Y_5 present on adjacent carbon atoms can constitute a methylenedioxy group;

30

wherein each X is independently S; O; or NR_3 ;

35

wherein R_1 is -H; - NO_2 ; -CN; straight chained or

-243-

5 branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; $-N(R_3)_2$; $-OR_3$; $-(CH_2)_pOR_3$; $-COR_3$; $-CO_2R_3$; $-CON(R_3)_2$ or $-CO_2(CH_2)_nV$;

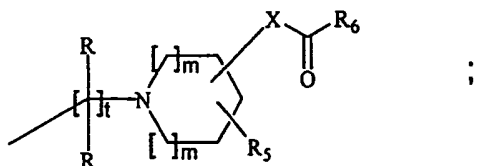
10 wherein R_2 is $-H$; straight chained or branched C_1-C_7 alkyl, hydroxyalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C_3-C_{10} cycloalkyl- C_1-C_{10} -alkyl, C_3-C_{10} cycloalkyl- C_1-C_{10} -monofluoroalkyl or C_3-C_{10} cycloalkyl- C_1-C_{10} -polyfluoroalkyl; $-CN$; $-CH_2XR_3$,
 15 $-CH_2X(CH_2)_pNHR_3$, $-(CH_2)_nNHR_3$, $-CH_2X(CH_2)_pN(R_3)_2$, $-CH_2X(CH_2)_pN_3$, or $-CH_2X(CH_2)_pNHCXR_7$; $-OR_3$; or wherein R_1 and R_2 together form a lactone ring;

20 wherein each R_3 is independently $-H$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; C_3-C_7 cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;
 25

wherein R_4 is

(i)

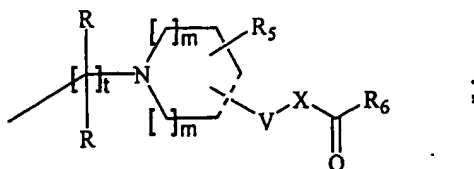
30



35

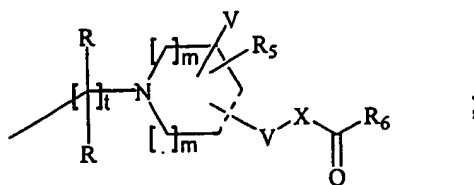
- 244 -

(ii)



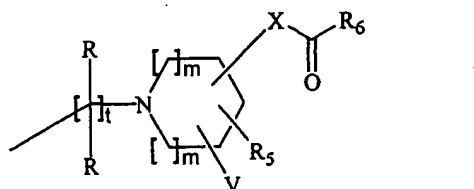
5

(iii)



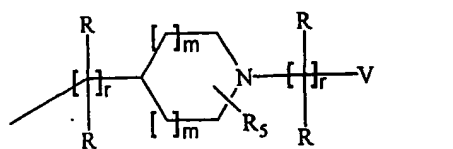
10

(iv)



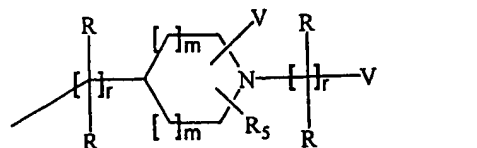
15

(v)



25

(vi)

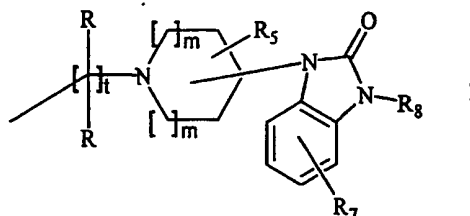


30

35

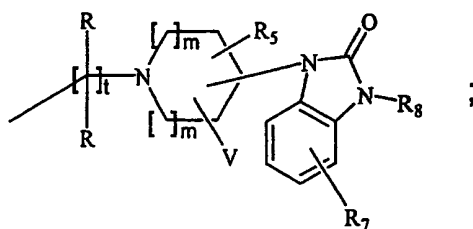
-245-

(vii)



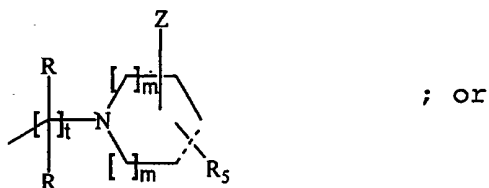
5

(viii)



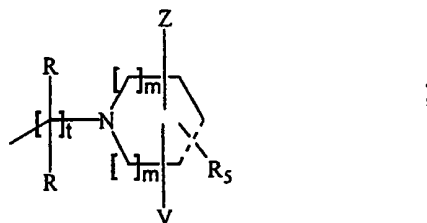
10

(ix)



15

(x)



20

25

wherein the dashed line represents a single bond or a double bond;

30

wherein each R is independently $-H$; $-F$; straight chained or branched C_1-C_7 alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C_2-C_7 alkenyl or alkynyl; $-N(R_3)_2$; $-NO_2$; $-CN$; $-CO_2R_3$; $-OR_3$; or $-CON(R_3)_2$;

35

wherein each V is independently aryl or heterocaryl, optionally substituted with one or more F ; Cl ; Br ; I ;

-246-

COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
-SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched
C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl,
aminoalkyl, or carboxamidoalkyl; straight chained or
5 branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight chained
10 or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
15 -CON(R₃)₂; aryl or heteroaryl, wherein the aryl or
heteroaryl is optionally substituted with one or more
F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
-N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight
20 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

25 wherein R₆ is -H; straight chained or branched C₁-C₇
alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl
or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -
30 CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, optionally
substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃;
-CON(R₃)₂; CN; -NO₂;
-N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight
35 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;

-247-

straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

5 wherein R₇ is H; F; Cl; Br; I; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
10 cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

wherein R₈ is independently straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or
15 polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

20 wherein Z is naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, phthalazinyl, quinoxalinyl, indolyl, benzo[b]furanyl, or benzo[b]thiophenyl; wherein the naphthyl, quinolinyl, isoquinolinyl, quinazolinyl, phthalazinyl, quinoxalinyl, indolyl, benzo[b]furanyl,
25 or benzo[b]thiophenyl may be substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched

C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or
30 branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

35 wherein each m is independently an integer from 0 to

-248-

3 inclusive;

wherein each n is independently an integer from 0 to 5 inclusive;

5

wherein each p is independently an integer from 1 to 7 inclusive;

wherein q is an integer from 1 to 3 inclusive;

10

wherein r is an integer from 0 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

15

or a pharmaceutically acceptable salt thereof.

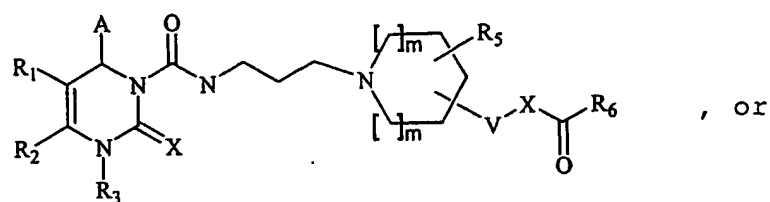
2. A (+) enantiomer of the compound of claim 1.

3. A (-) enantiomer of the compound of claim 1.

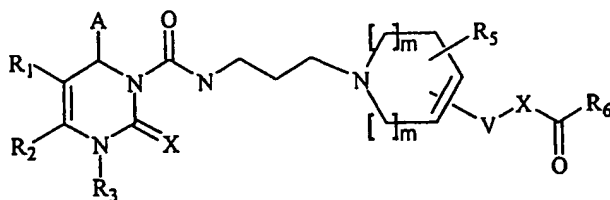
20

4. The compound of claim 1 having the structure:

25



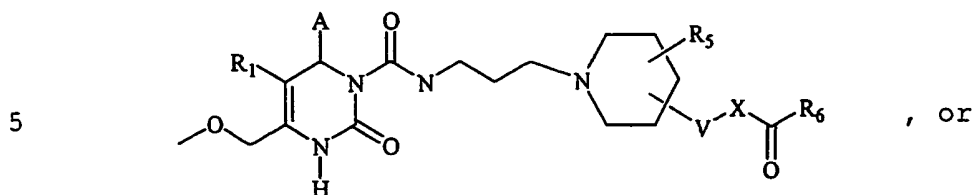
30



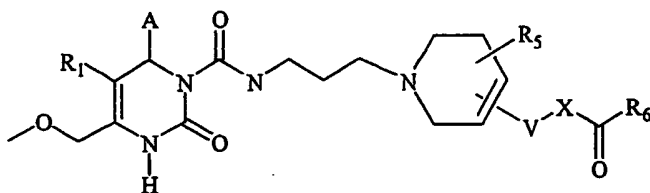
35

-249-

5. The compound of claim 4 having the structure:

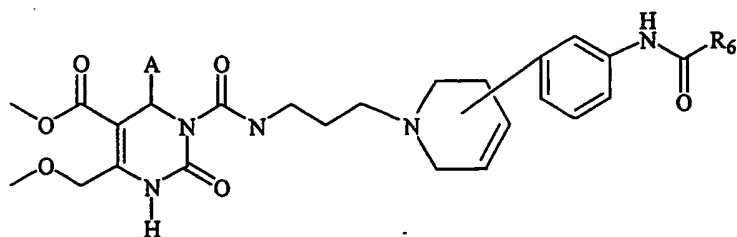
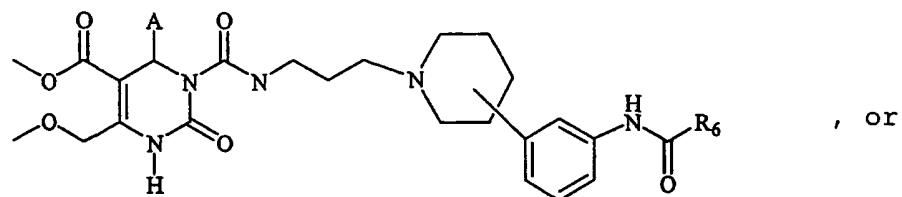


10



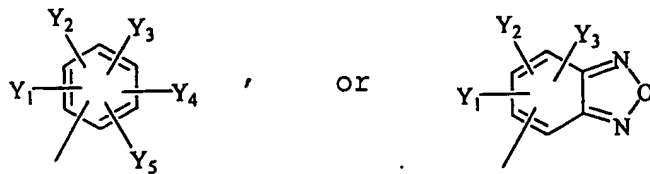
15

6. The compound of claim 5, having the structure:

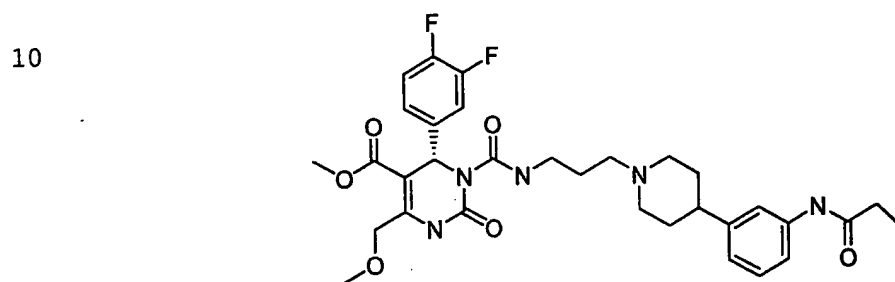


-250-

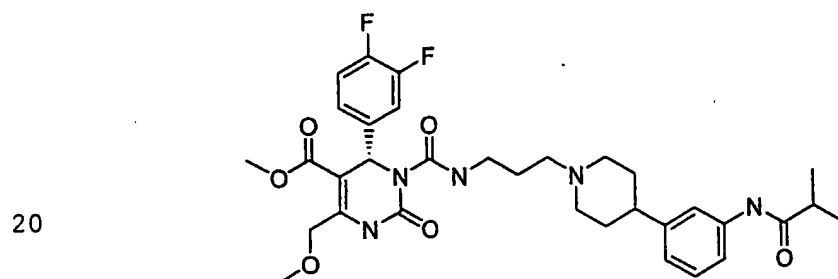
7. The compound of claim 6, wherein A is



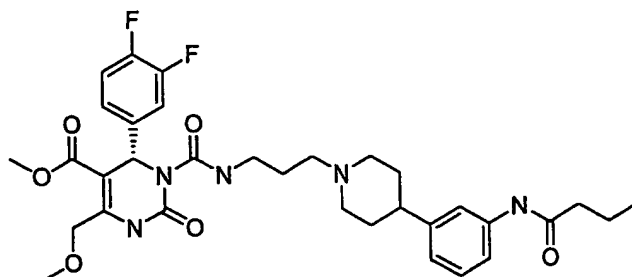
8. The compound of claim 7, wherein the compound is



15



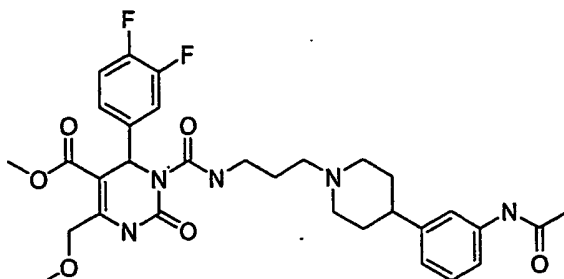
25



30

-251-

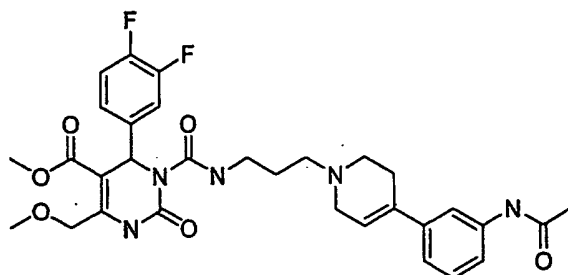
5



; or

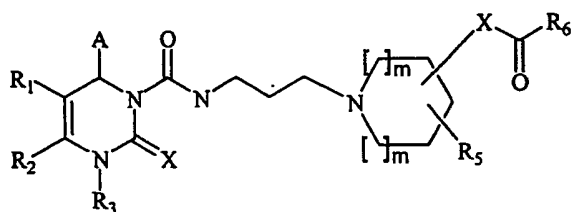
10

15



9. The compound of claim 1, wherein the compound has the structure:

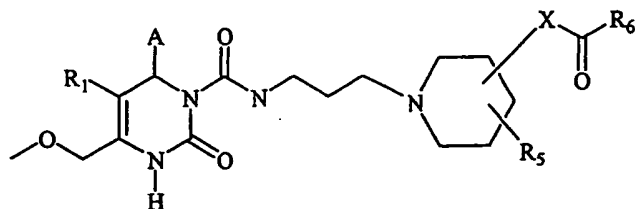
20



25

10. The compound of claim 9, wherein the compound has the structure:

30

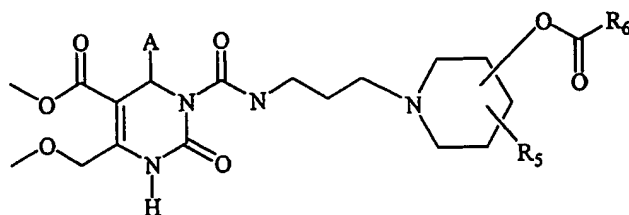


35

-252-

11. The compound of claim 10, wherein the compound has the structure:

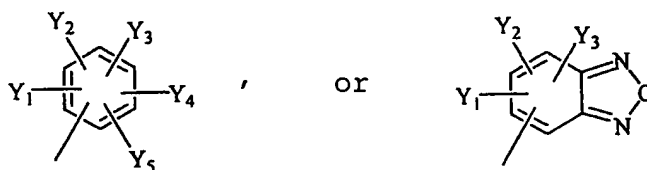
5



10

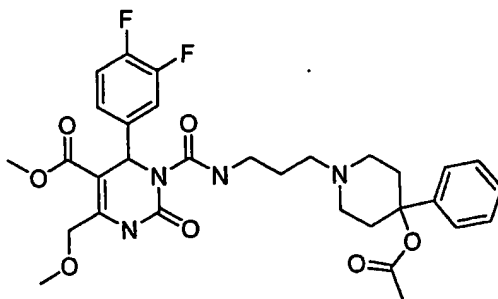
12. The compound of claim 11, wherein A is

20



13. The compound of claim 12 having the structure:

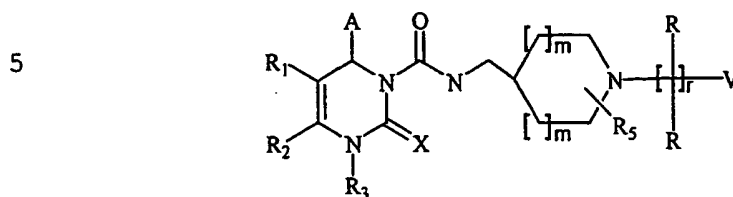
30



35

-253-

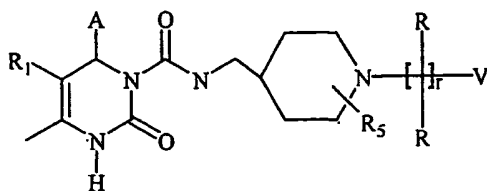
14. The compound of claim 1, having the structure:



10

15. The compound of claim 14, having the structure:

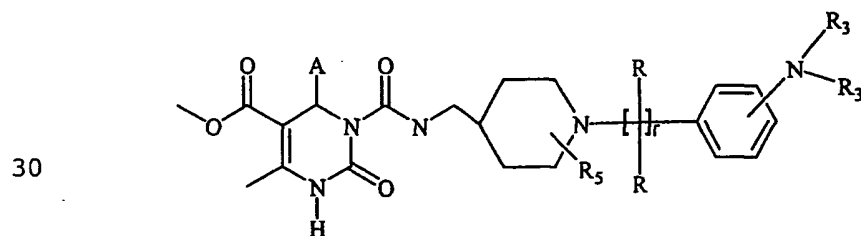
15



20

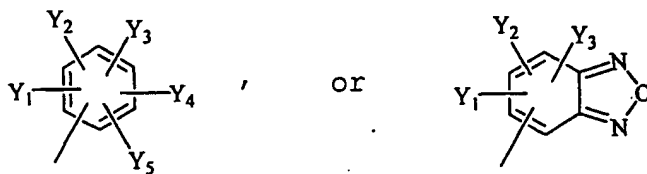
16. The compound of claim 15 having the structure:

25

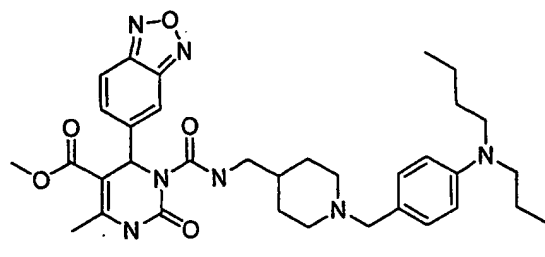


-254-

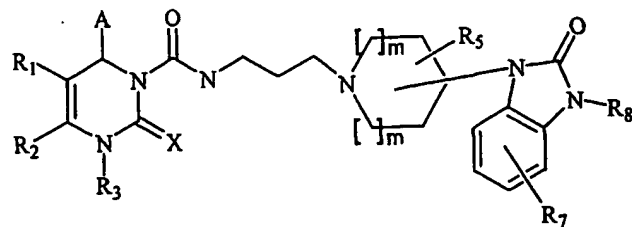
17. The compound of claim 16 wherein A is



18. The compound of claim 17 having the structure:

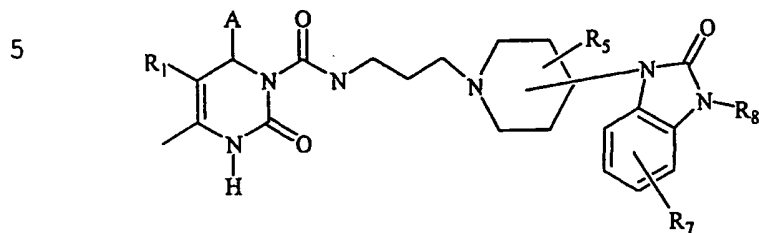


19. The compound of claim 1 having the structure:

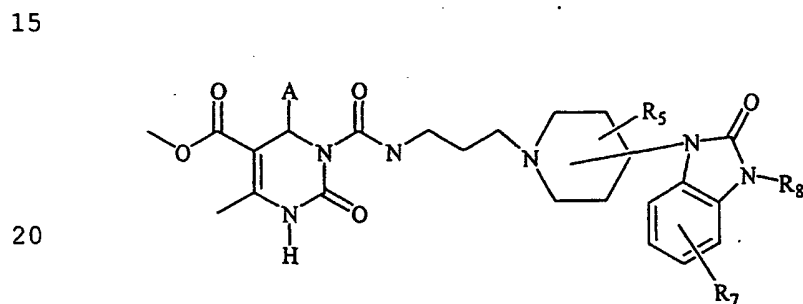


-255-

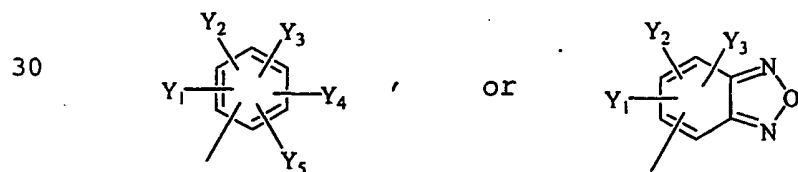
20. The compound of claim 19 having the structure:



21. The compound of claim 20 having the structure:

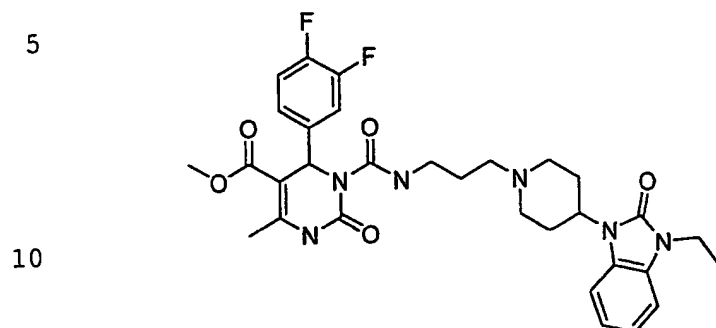


22. The compound of claim 21 wherein A is

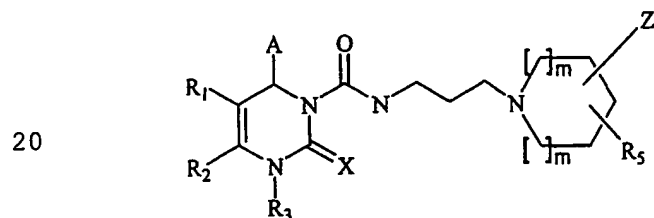


-256-

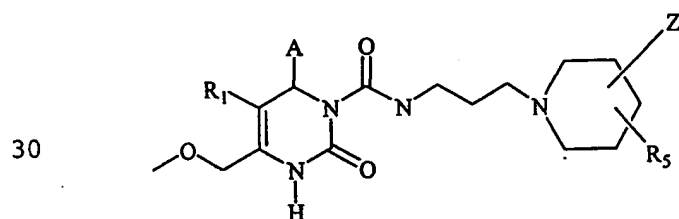
23. The compound of claim 22 having the structure



15 24. The compound of claim 1 having the structure:



25. The compound of claim 24 having the structure:

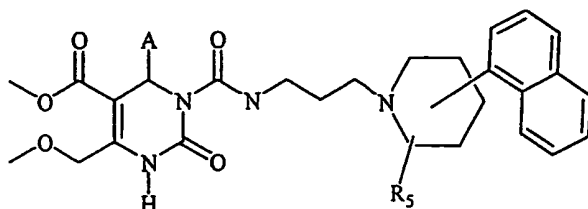


-257-

26. The compound of claim 25 having the structure:

5

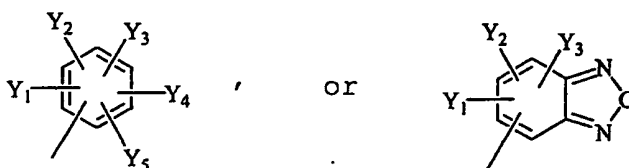
10



27. The compound of claim 26 wherein A is

15

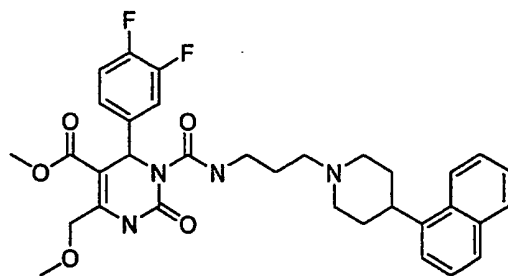
20



28. The compound of claim 27 having the structure:

25

30

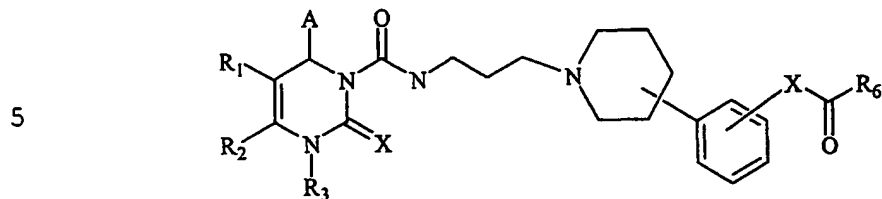


35

29. The compound of claim 1, wherein the compound is
(+)-1,2,3,6-tetrahydro-1-{n-[4-(3,-acetamido)-phenyl
-piperidin-1-yl]propyl}carboxamido-4-methoxymethyl-
6-(3,4-difluoro-phenyl)-2-oxypyrimidine-5-
carboxylic acid methyl ester.

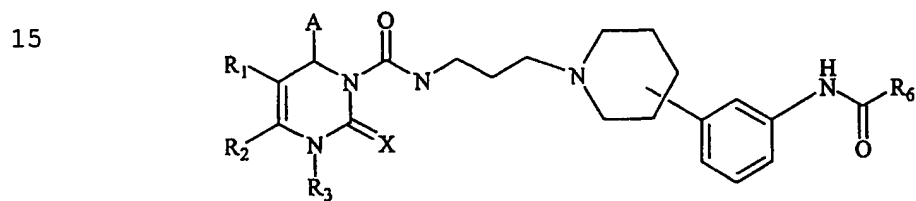
-258-

30. The compound of claim 4 having the structure:



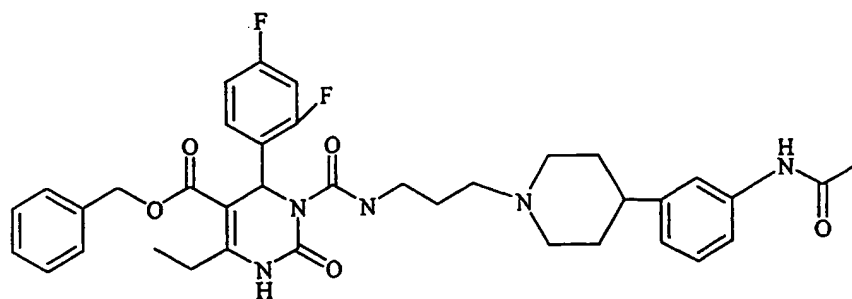
10

31. The compound of claim 30 having the structure:



20

32. The compound of claim 31 having the structure:

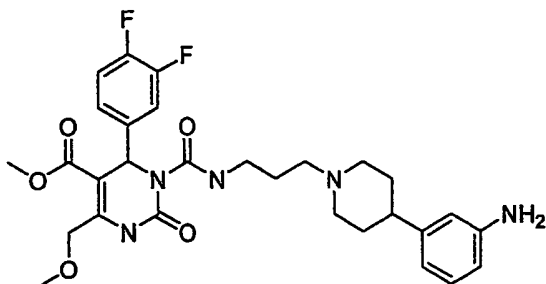


25

-259-

33. A compound having the structure:

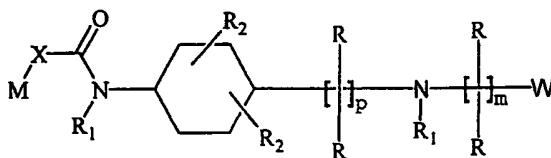
5



10

34. A compound having the structure:

15



20

wherein each R is independently -H; -F; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -SR₃; -CO₂R₃; or
-OR₃;

wherein each R₁ is independently -H; straight chained
or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

wherein each R₂ is -H; -NO₂; -N₃; -CN; straight chained
or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇

-260-

alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; or aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R₃ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein M is aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein X is (CH₂)_n, O, S or NR₃;

wherein W is

(a) C₃-C₇ cycloalkyl, monofluorocycloalkyl,

-261-

polyfluorocycloalkyl or cycloalkenyl
optionally substituted with one or more
COR₃; CO₂R₃;
-CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
5 (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or
branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇
10 cycloalkyl; or

(b) aryl or heteroaryl optionally substituted
with one or more F; Cl; Br; I; COR₃; CO₂R₃;
-CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
15 (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or
carboxamidoalkyl; straight chained or
branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇
20 cycloalkyl;

wherein m is an integer from 0 to 4 inclusive;

25 wherein n is an integer from 0 to 6 inclusive;

wherein p is an integer from 1 to 4 inclusive;

wherein q is an integer from 1 to 3 inclusive;

30 or a pharmaceutically acceptable salt thereof.

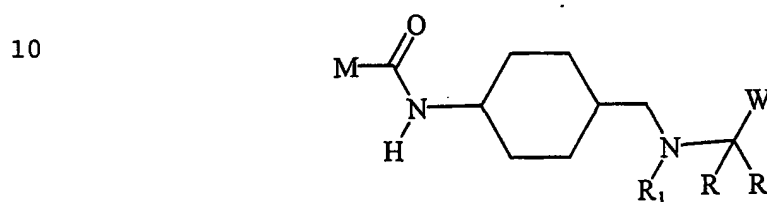
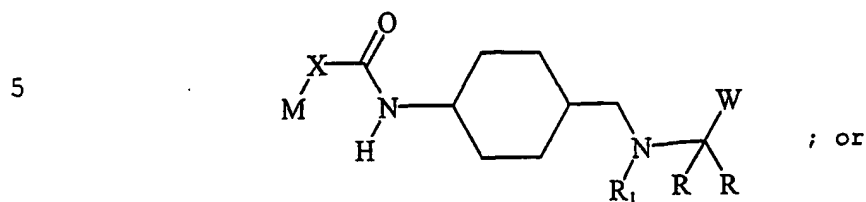
35. A (+) enantiomer of the compound of claim 34.

36. A (-) enantiomer of the compound of claim 34.

35

-262-

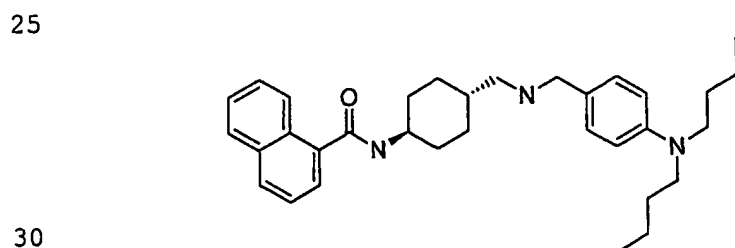
37. The compound of claim 34 having the structure:



38. The compound of claim 37, wherein W is phenyl optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; or (CH₂)_qSR₃.

20

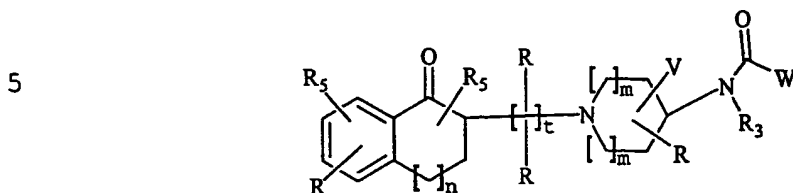
39. The compound of claim 38 having the structure



35

-263-

40. A compound having the structure:



10 wherein each R is independently -H; -F; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃; or -CON(R₃)₂;

15 wherein each R₁ is independently -H; F; Cl; Br; I; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

20

25

30

wherein each R₃ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇

35

-264-

alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

5 wherein R₅ is -H; -NO₂; -N₃; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or
10 cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; aryl or heteroaryl, wherein the aryl or heteroaryl is optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight
15 chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

20 wherein V is H; aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or branched C₁-
25 C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

30

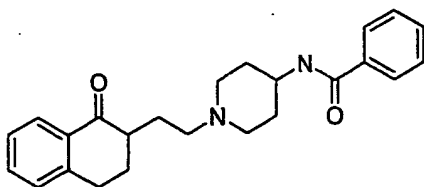
wherein W is

(a) C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl
35 optionally substituted with one or more

-267-

45. A compound of claim 43 wherein W is phenyl optionally substituted with one or more F; Cl; Br; I; COR_3 ; CO_2R_3 ; $-\text{CON}(\text{R}_3)_2$; CN; $-\text{NO}_2$; $-\text{N}(\text{R}_3)_2$; $-\text{OR}_3$; $-\text{SR}_3$; $(\text{CH}_2)_q\text{OR}_3$; $(\text{CH}_2)_q\text{SR}_3$; or straight chained or branched C_1 - C_7 alkyl groups.

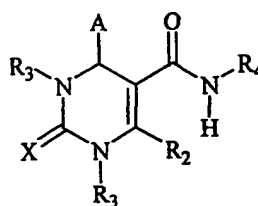
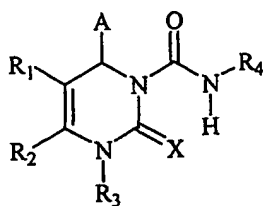
46. A compound of claim 45 having the structure



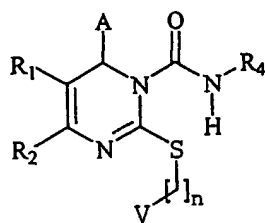
-268-

47. A method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject wherein the compound has the structure:having the structure:

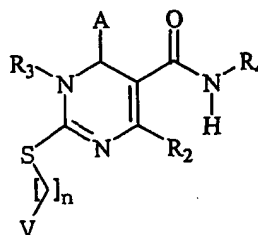
10



15



, or



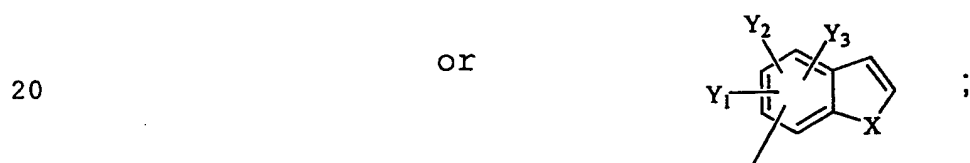
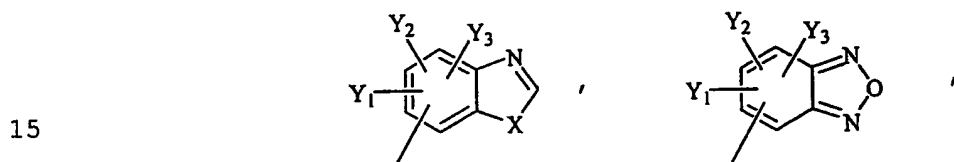
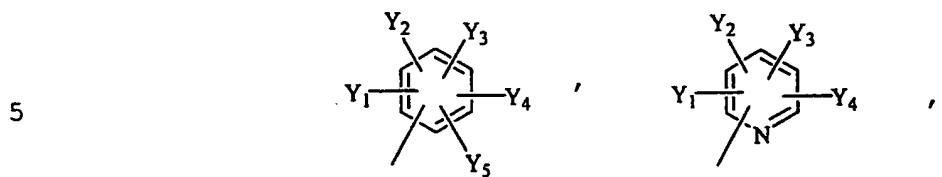
20

25

30

-269-

wherein A is



25

wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently
 -H; straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl or polyfluoroalkyl; straight chained
 or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
 cycloalkyl, monofluorocycloalkyl,
 polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br,
 or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CON(R₃)₂,
 30 or -COOR₃; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present
 on adjacent carbon atoms can constitute a
 methylenedioxy group;

35

wherein each X is independently S; O; or NR₃;

-270-

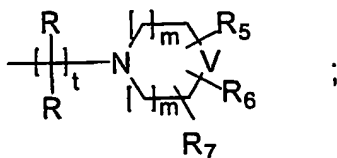
wherein R_1 is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; or -CO₂(CH₂)_nV;

wherein R_2 is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₅; -OR₃; or wherein R_1 and R_2 together form a lactone ring;

wherein each R_3 is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

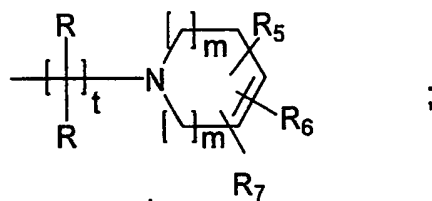
wherein R_4 is

(i)

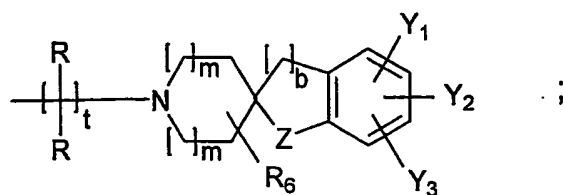


35

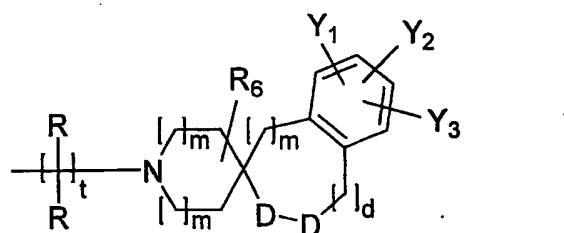
(ii)



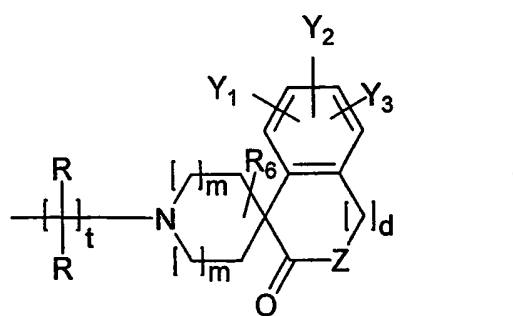
(iii)



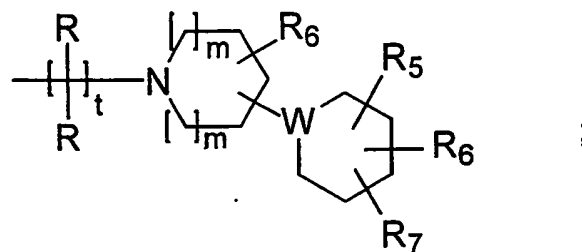
(iv)



(v)



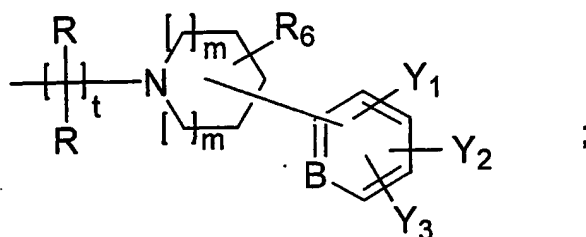
(vi)



(vii)

5

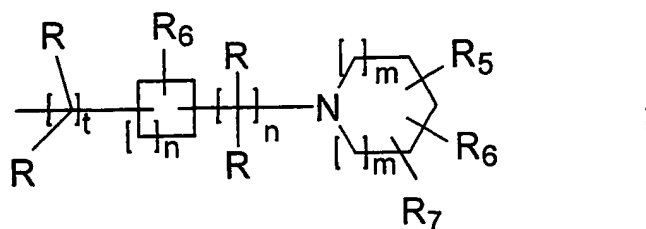
10



15

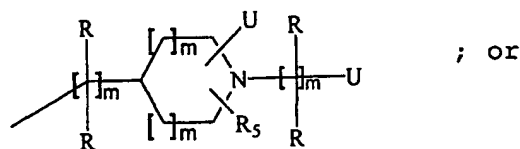
(viii)

20



25

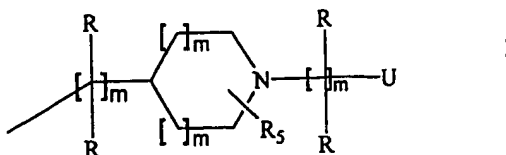
(ix)



; or

30

(x)



35

-273-

5 wherein each R is independently -H; -F; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃;
or -CN(R₃)₂;

wherein B is N or CY₄;

10 wherein each D is independently C(R₃)₂; O; S; NR₃;
CO; or CS;

15 wherein each U is independently aryl or heteroaryl,
optionally substituted with one or more F; Cl; Br;
I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
-SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
20 polyfluorocycloalkyl or cycloalkenyl;

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

25 wherein W is CR₅; CR₆ or N;

wherein Z is S; O; C(R₃)₂; or NR₃;

30 wherein each R₅ is -H; -NO₂; -N₃; -CN; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein
35 the aryl or heteroaryl is optionally substituted

-274-

with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
5 straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein each R₆ is independently -H; straight chained
10 or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl, alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃;
15 -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

wherein R₇ is -H; aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
20 (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl, polyfluoroalkyl, or aminoalkyl; straight chained or branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
25 polyfluorocycloalkyl or cycloalkenyl;

wherein R₈ is -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
30 polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; aryl or heteroaryl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
35 -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight

-275-

chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

wherein b is 1 or 2;

wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to
3 inclusive;

wherein each n is independently an integer from 0 to
5 inclusive;

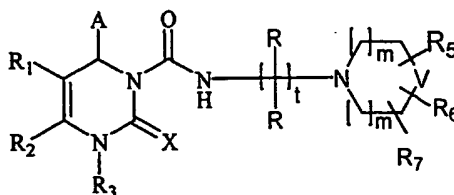
wherein each p is independently an integer from 1 to
7 inclusive;

wherein q is an integer from 1 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

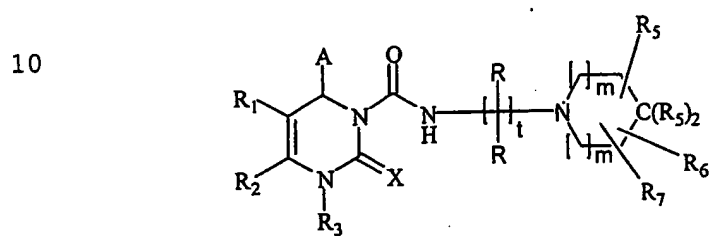
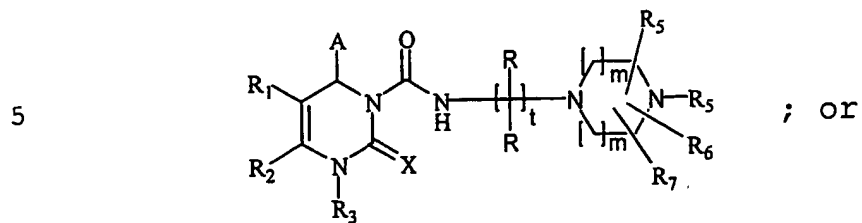
or a pharmaceutically acceptable salt thereof.

48. The method of claim 47, wherein the compound has the
structure



-276-

49. The method of claim 48, wherein the compound has the structure



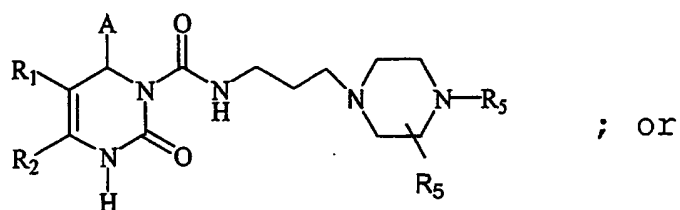
15

20

-277-

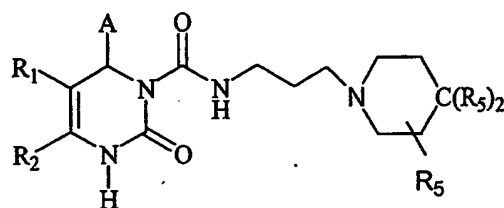
50. The method of claim 49, wherein the compound has the structure

5



10

15

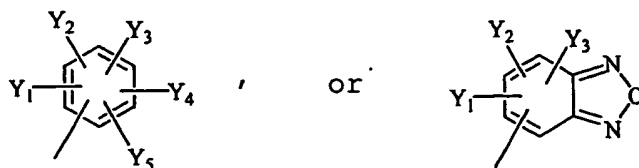


51. The method of claim 50, wherein at least one R_5 group is an aryl or heteroaryl group optionally substituted with one or more F; Cl; Br; I; $-\text{NO}_2$; $-\text{N}(\text{R}_3)_2$; $-\text{OR}_3$; $-\text{XCOR}_8$; or straight chained or branched C_1 - C_7 alkyl.

25

52. The method of claim 51, wherein A is:

30

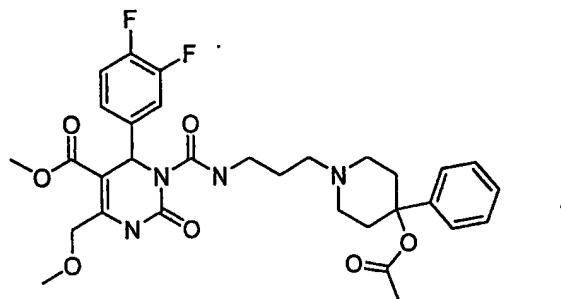


-278-

53. The method of claim 52, wherein the compound is selected from the group consisting of:

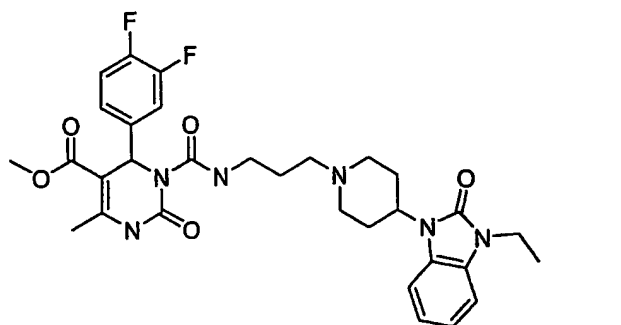
5

(a)



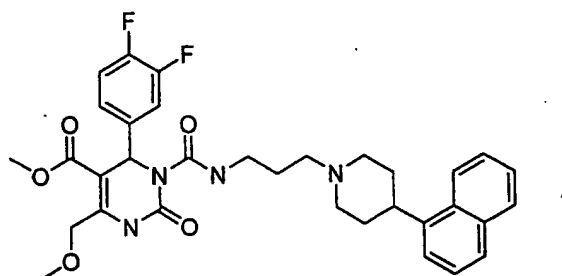
10

(b)



15

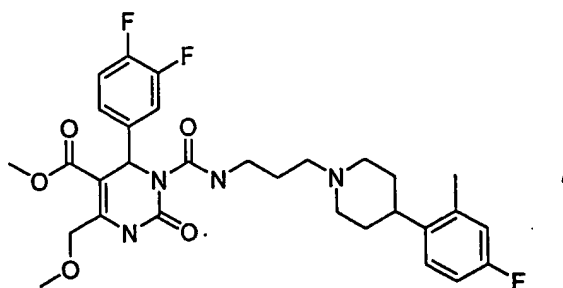
(c)



20

25

(d)



30

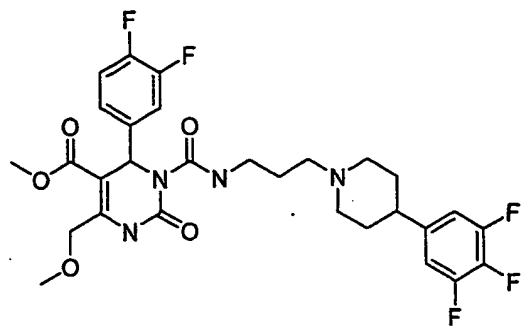
35

-279-

(e)

5

10

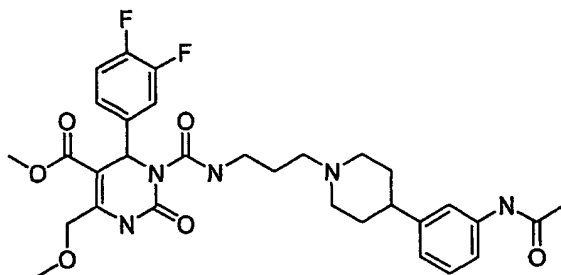


; and

(f)

15

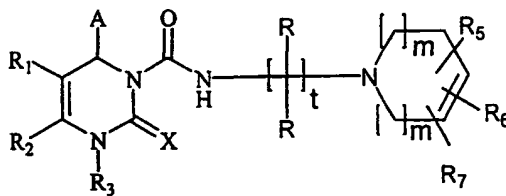
20



54. The method of claim 47, wherein the compound has the structure

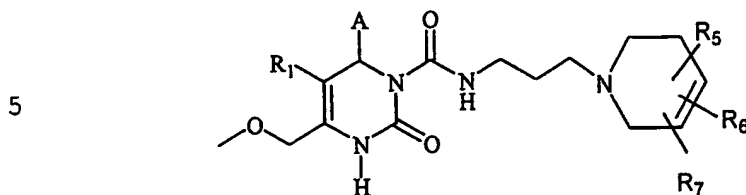
25

30

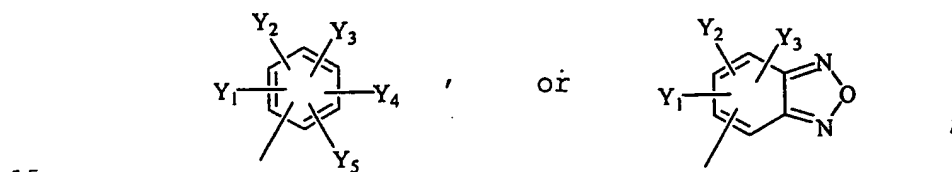


-280-

55. The method of claim 54, wherein the compound has the structure



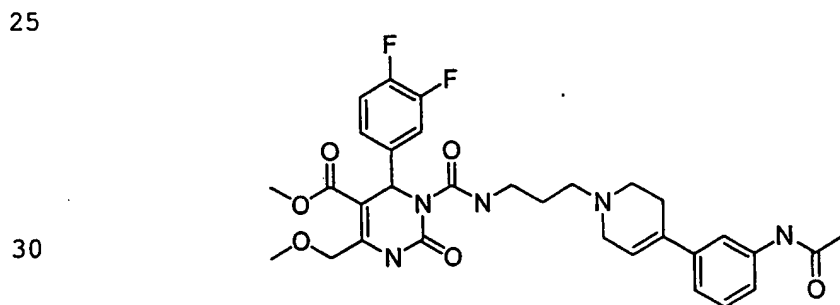
- 10 56. The method of claim 55, wherein A is



and R₇ is phenyl, optionally substituted with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; or straight chained or branched C₁-C₇ alkyl.

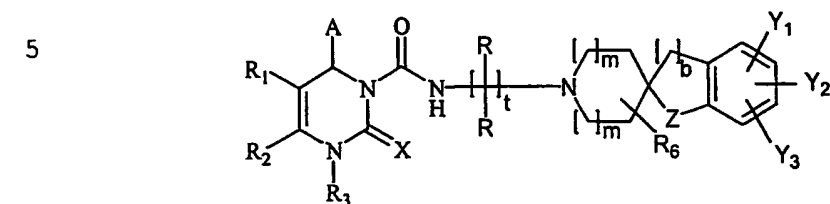
20

57. The method of claim 56, wherein the compound has the structure



-281-

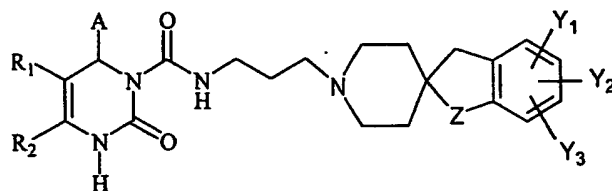
58. The method of claim 47, wherein the compound has the structure



10

59. The method of claim 58, wherein the compound has the structure

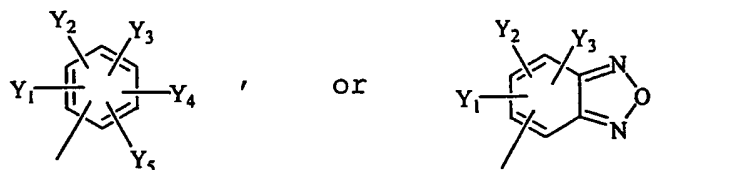
15



20

60. The method of claim 59, wherein A is

25



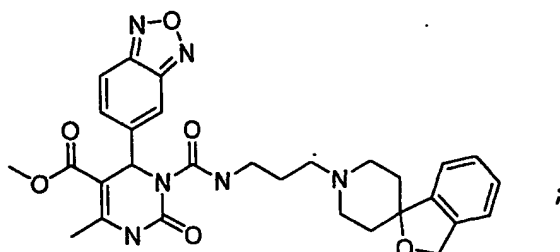
30

and Z is O or CH₂.

-282-

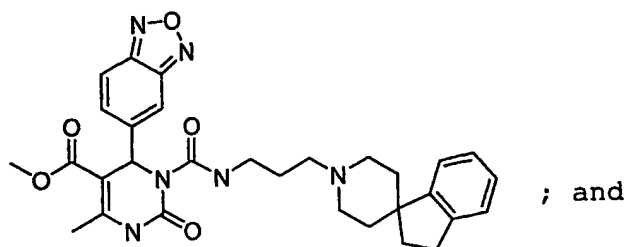
61. The method of claim 60, wherein the compound is selected from the group consisting of

5



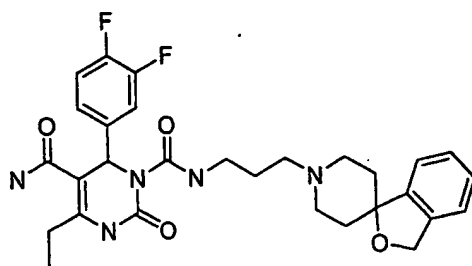
10

15



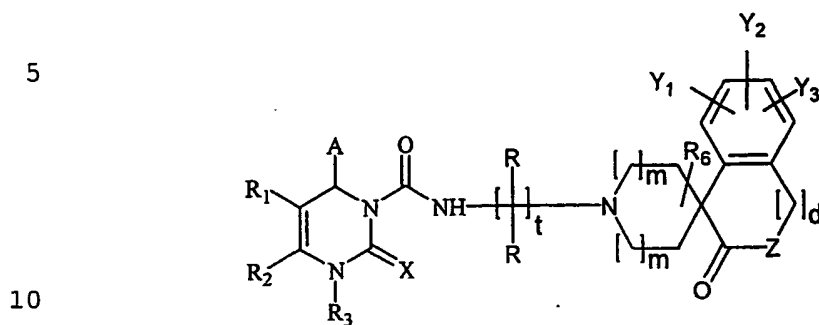
20

25

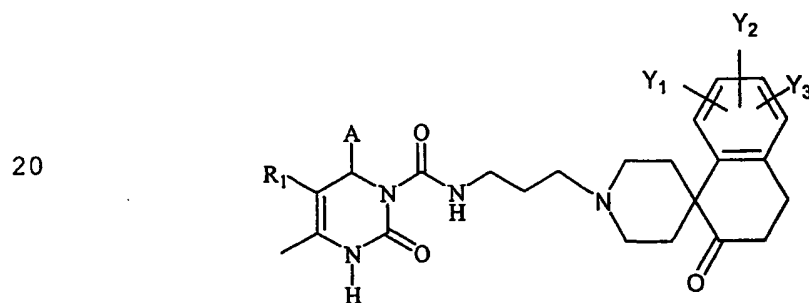


-283-

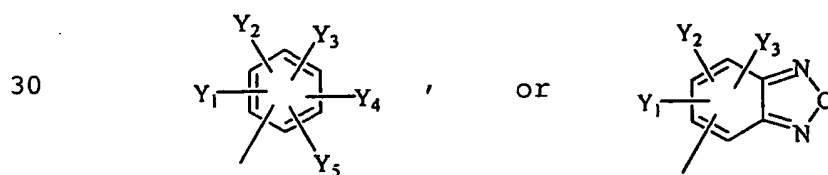
62. The method of claim 47, wherein the compound has the structure



63. The method of claim 62, wherein the compound has the structure

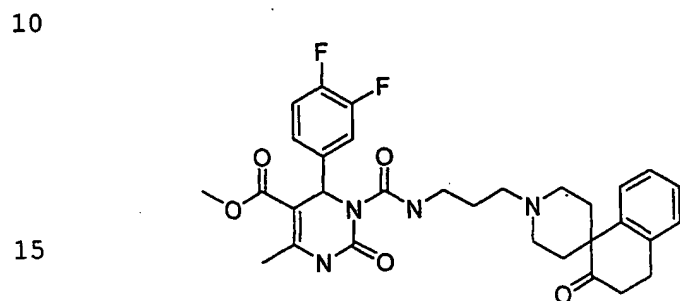
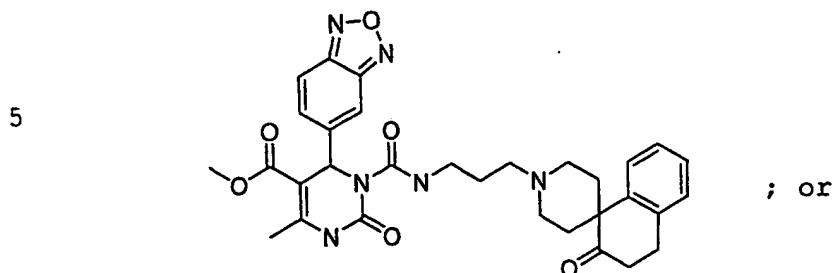


64. The method of claim 63, wherein A is

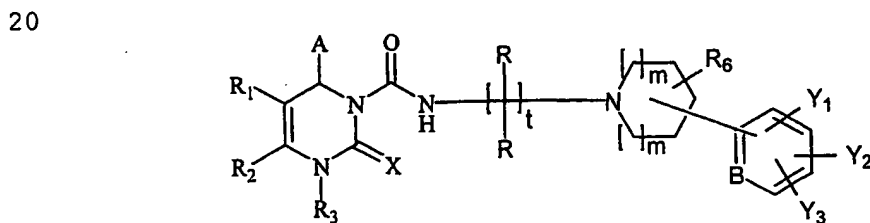


-284-

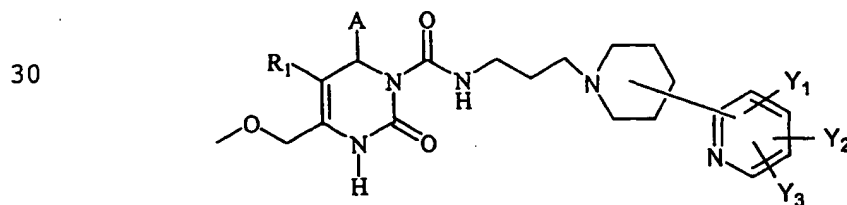
65. The method of claim 64, wherein the compound is



66. The method of claim 47, wherein the compound has the structure

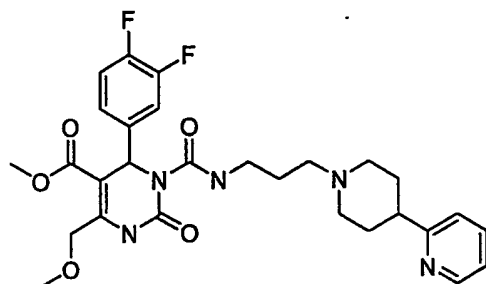


67. The method of claim 66, wherein the compound has the structure

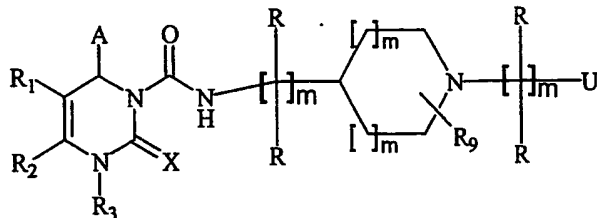


-285-

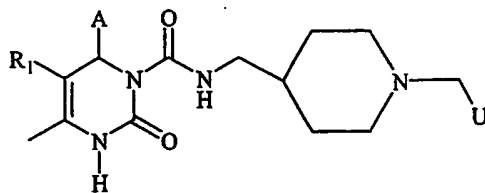
68. The method of claim 67, wherein the compound has the structure



69. The method of claim 47, wherein the compound has the structure
- 15

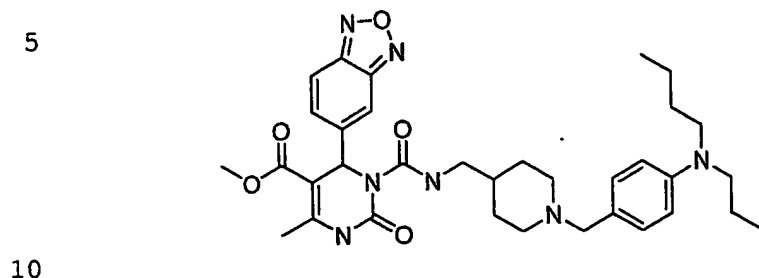


70. The method of claim 69, wherein the compound has the structure
- 25

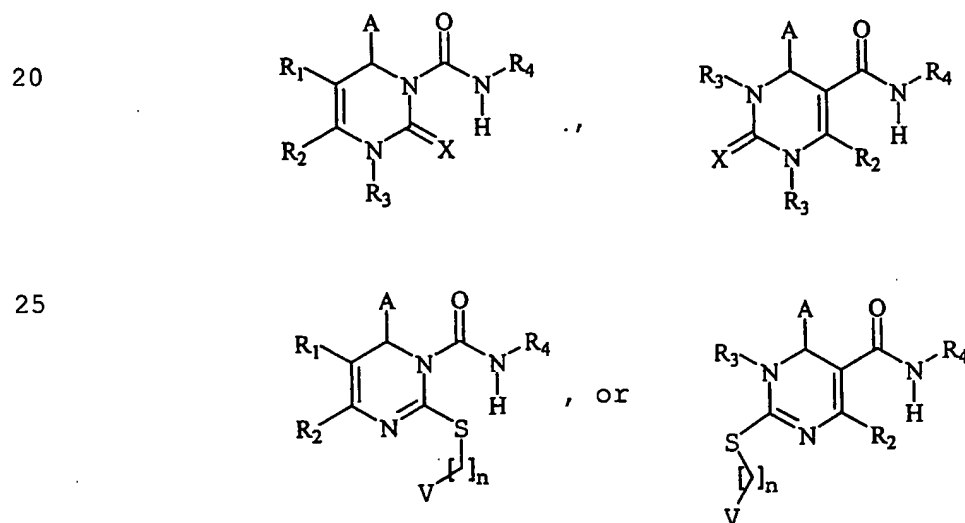


-286-

71. The method of claim 70, wherein the compound has the structure

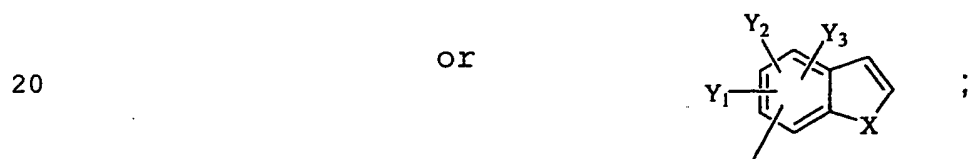
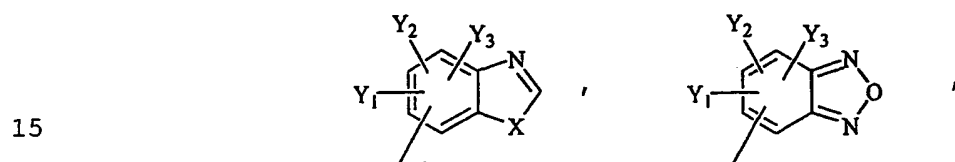
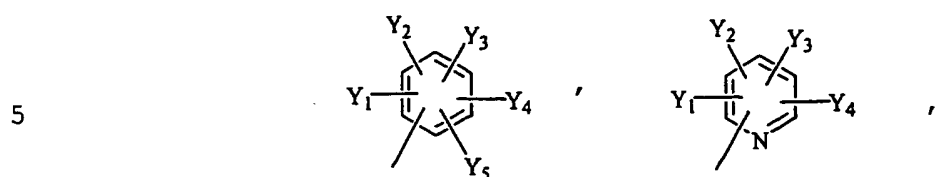


72. A method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound effective to reduce the body mass of the subject wherein the compound has the structure:
- 15



-287-

wherein A is



25

wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br, or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CON(R₃)₂, or -COOR₃; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present on adjacent carbon atoms can constitute a methylenedioxy group;

30

35

wherein each X is independently S; O; or NR₃;

-288-

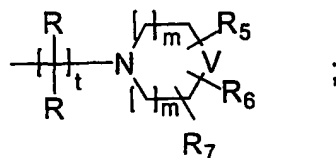
wherein R_1 is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; or -CO₂(CH₂)_nV;

wherein R_2 is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₅; -OR₃; or wherein R_1 and R_2 together form a lactone ring;

wherein each R_3 is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_4 is

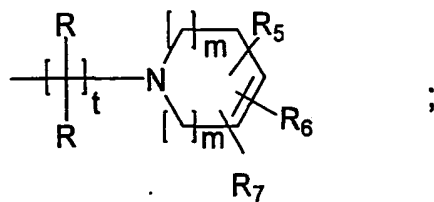
(i)



35

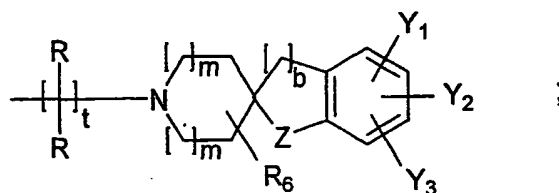
-289-

(ii)



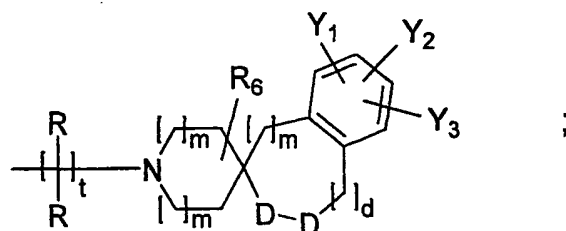
5

(iii)



10

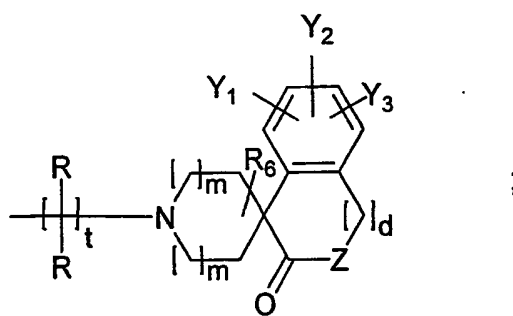
(iv)



15

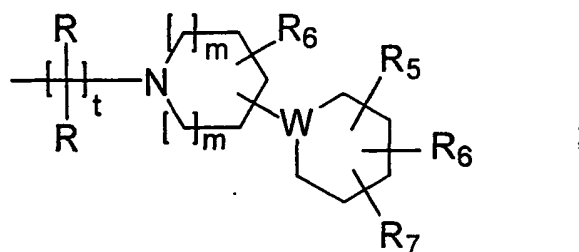
20

(v)



25

(vi)



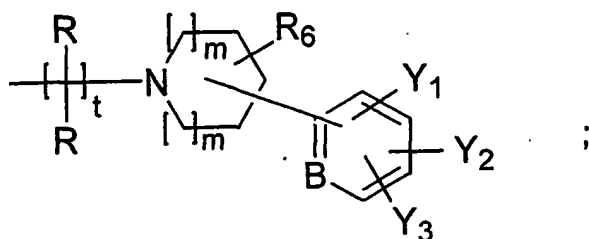
30

35

(vii)

5

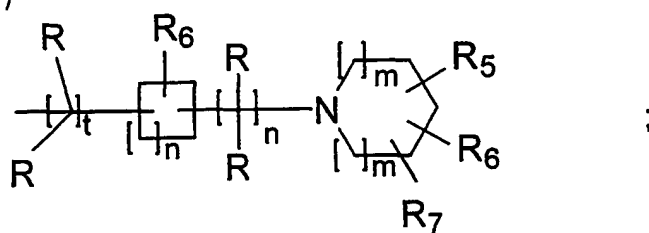
10



15

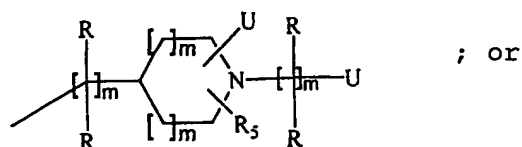
(viii)

20



(ix)

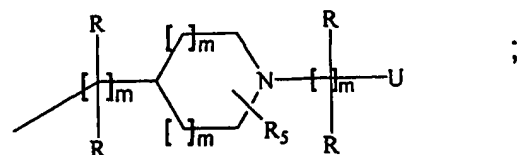
25



; or

(x)

30



35

-291-

wherein each R is independently -H; -F; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃;
5 or -CN(R₃)₂;

wherein B is N or CY₄;

wherein each D is independently C(R₃)₂; O; S; NR₃;
10 CO; or CS;

wherein each U is independently aryl or heteroaryl,
optionally substituted with one or more F; Cl; Br;
I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
15 -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
20 polyfluorocycloalkyl or cycloalkenyl;

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

wherein W is CR₅; CR₆ or N;

25

wherein Z is S; O; C(R₃)₂; or NR₃;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
30 polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein
35 the aryl or heteroaryl is optionally substituted

-292-

with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃;
-XCOR₈; straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
5 straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

wherein each R₆ is independently -H; straight chained
10 or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl,
alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃;
15 -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

wherein R₇ is -H; aryl or heteroaryl, optionally
substituted with one or more F; Cl; Br; I; COR₃;
CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
20 (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, or aminoalkyl; straight chained or
branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇
cycloalkyl, monofluorocycloalkyl,
25 polyfluorocycloalkyl or cycloalkenyl;

wherein R₈ is -H; straight chained or branched C₁-C₇
alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
30 cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃;
-(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; aryl or
heteroaryl, optionally substituted with one or more
F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
35 -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight

-293-

5 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

wherein b is 1 or 2;

10 wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to
3 inclusive;

15 wherein each n is independently an integer from 0 to
5 inclusive;

wherein each p is independently an integer from 1 to
7 inclusive;

20 wherein q is an integer from 1 to 3 inclusive;

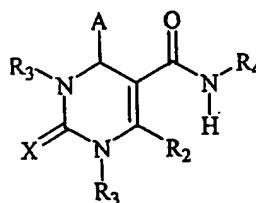
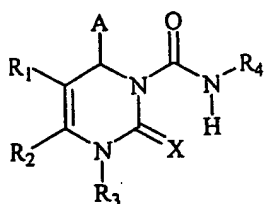
wherein t is an integer from 2 to 6 inclusive;

25 or a pharmaceutically acceptable salt thereof.

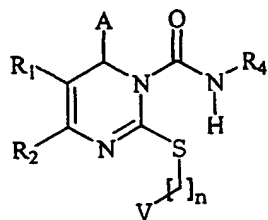
-294-

73. A method of treating a subject suffering from depression and/or anxiety which comprises administering to the subject an amount of a compound effective to treat the subject's depression and/or anxiety wherein the compound has the structure:

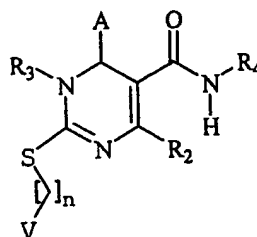
10



15



, or



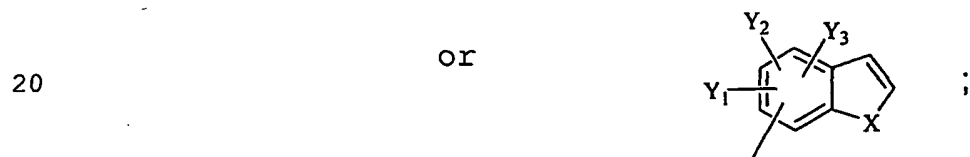
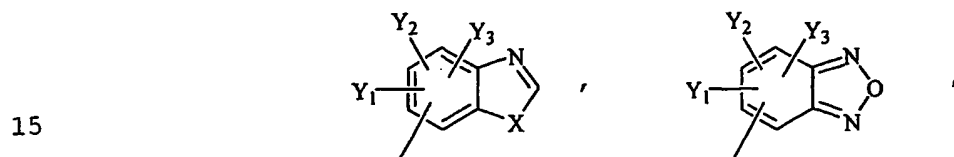
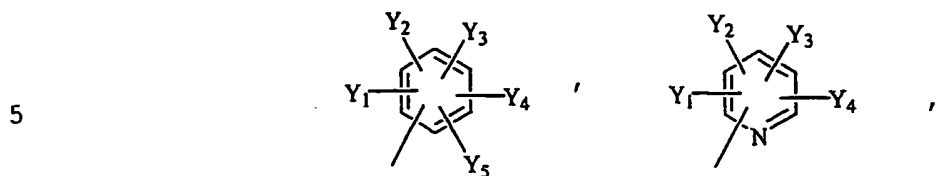
20

25

30

-295-

wherein A is



25

wherein each of Y₁, Y₂, Y₃, Y₄ and Y₅ is independently
 -H; straight chained or branched C₁-C₇ alkyl,
 monofluoroalkyl or polyfluoroalkyl; straight chained
 or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
 cycloalkyl, monofluorocycloalkyl,
 polyfluorocycloalkyl or cycloalkenyl; -F, -Cl, -Br,
 or -I; -NO₂; -N₃; -CN; -OR₃, -OCOR₃, -COR₃, -CON(R₃)₂,
 30 or -COOR₃; or any two of Y₁, Y₂, Y₃, Y₄ and Y₅ present
 on adjacent carbon atoms can constitute a
 methylenedioxy group;

35

wherein each X is independently S; O; or NR₃;

-296-

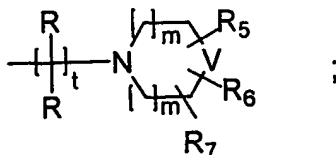
wherein R_1 is -H; -NO₂; -CN; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃; -CON(R₃)₂; or -CO₂(CH₂)_nV;

wherein R_2 is -H; straight chained or branched C₁-C₇ alkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl; C₃-C₁₀ cycloalkyl-C₁-C₁₀-alkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀-monofluoroalkyl or C₃-C₁₀ cycloalkyl-C₁-C₁₀-polyfluoroalkyl; -CN; -CH₂XR₃, -CH₂X(CH₂)_pNHR₃, -(CH₂)_nNHR₃, -CH₂X(CH₂)_pN(R₃)₂, -CH₂X(CH₂)_pN₃, or -CH₂X(CH₂)_pNHCXR₅; -OR₃; or wherein R_1 and R_2 together form a lactone ring;

wherein each R_3 is independently -H; straight chained or branched C₁-C₇ alkyl, monofluoroalkyl or polyfluoroalkyl; straight chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl, polyfluorocycloalkyl or cycloalkenyl;

wherein R_4 is

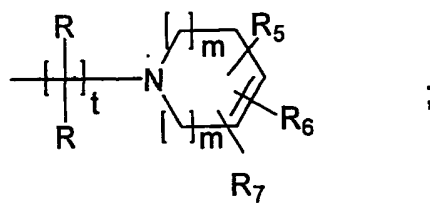
(i)



35

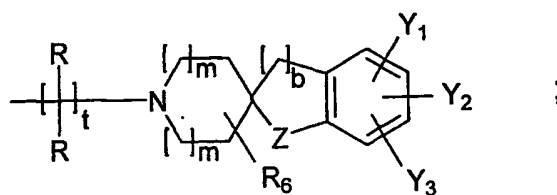
-297-

(ii)



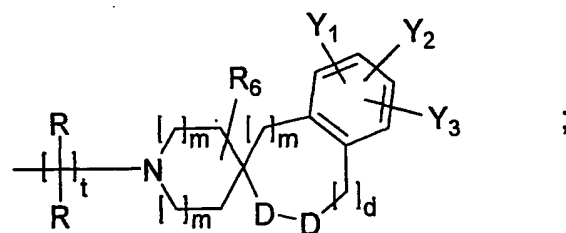
5

(iii)



10

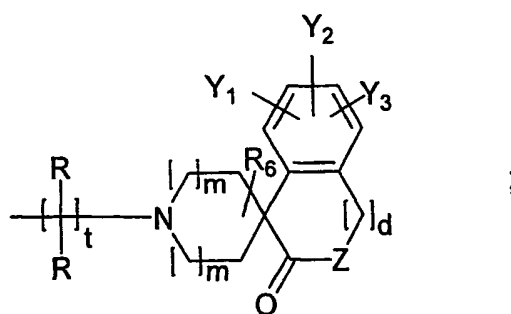
(iv)



15

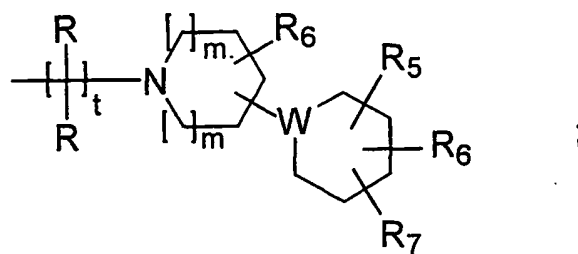
20

(v)



25

(vi)

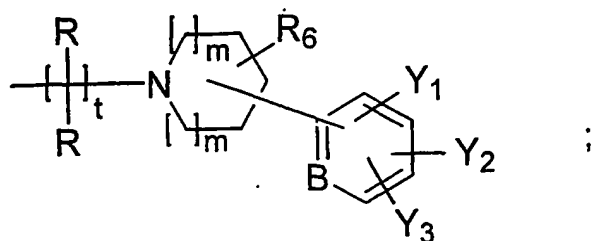


35

(vii)

5

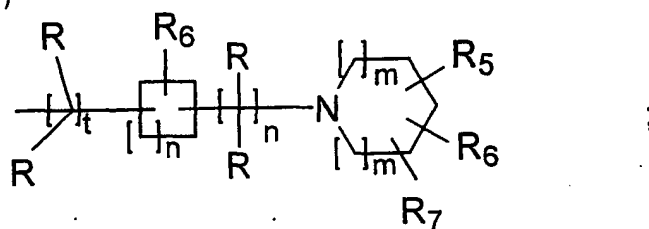
10



15

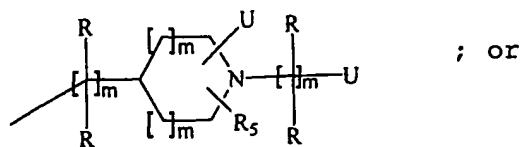
(viii)

20



(ix)

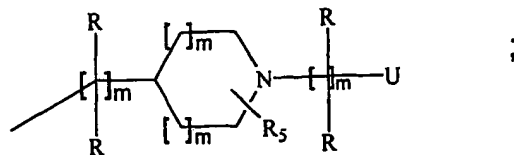
25



; or

(x)

30



;

35

-299-

wherein each R is independently -H; -F; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; -N(R₃)₂; -NO₂; -CN; -CO₂R₃; -OR₃;
5 or -CN(R₃)₂;

wherein B is N or CY₄;

wherein each D is independently C(R₃)₂; O; S; NR₃;
10 CO; or CS;

wherein each U is independently aryl or heteroaryl,
optionally substituted with one or more F; Cl; Br;
I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃;
15 -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
20 polyfluorocycloalkyl or cycloalkenyl;

wherein V is C(R₅)₂; CR₅R₆; NR₅ or NR₆;

wherein W is CR₅; CR₆ or N;

25

wherein Z is S; O; C(R₃)₂; or NR₃;

wherein each R₅ is -H; -NO₂; -N₃; -CN; straight
chained or branched C₁-C₇ alkyl, monofluoroalkyl or
polyfluoroalkyl; straight chained or branched C₂-C₇
alkenyl or alkynyl; C₃-C₇ cycloalkyl,
monofluorocycloalkyl, polyfluorocycloalkyl or
cycloalkenyl; -N(R₃)₂; -OR₃; -(CH₂)_pOR₃; -COR₃; -CO₂R₃;
30 or -CON(R₃)₂; -XCOR₈; or aryl or heteroaryl, wherein
35 the aryl or heteroaryl is optionally substituted

-300-

with one or more F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂;
CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃;
-XCOR₈; straight chained or branched C₁-C₇ alkyl,
monofluoroalkyl, polyfluoroalkyl, or aminoalkyl;
5 straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

wherein each R₆ is independently -H; straight chained
10 or branched C₁-C₇ alkyl, hydroxyalkyl, aminoalkyl,
alkoxyalkyl, monofluoroalkyl or polyfluoroalkyl;
straight chained or branched C₂-C₇ alkenyl or
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃;
15 -(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂;

wherein R₇ is -H; aryl or heteroaryl, optionally
substituted with one or more F; Cl; Br; I; COR₃;
CO₂R₃; -CON(R₃)₂; CN; -NO₂; -N(R₃)₂; -OR₃; -SR₃;
20 (CH₂)_qOR₃; (CH₂)_qSR₃; -XCOR₈; straight chained or
branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, or aminoalkyl; straight chained or
branched C₂-C₇ alkenyl, C₂-C₇ alkynyl; C₃-C₇
cycloalkyl, monofluorocycloalkyl,
25 polyfluorocycloalkyl or cycloalkenyl;

wherein R₈ is -H; straight chained or branched C₁-C₇
alkyl, monofluoroalkyl or polyfluoroalkyl; straight
chained or branched C₂-C₇ alkenyl or alkynyl; C₃-C₇
30 cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl; -N(R₃)₂; -OR₃;
-(CH₂)_pOR₃; -COR₃; -CO₂R₃; or -CON(R₃)₂; aryl or
heteroaryl, optionally substituted with one or more
F; Cl; Br; I; COR₃; CO₂R₃; -CON(R₃)₂; CN; -NO₂;
35 -N(R₃)₂; -OR₃; -SR₃; (CH₂)_qOR₃; (CH₂)_qSR₃; straight

-301-

5 chained or branched C₁-C₇ alkyl, monofluoroalkyl,
polyfluoroalkyl, aminoalkyl, or carboxamidoalkyl;
straight chained or branched C₂-C₇ alkenyl, C₂-C₇
alkynyl; C₃-C₇ cycloalkyl, monofluorocycloalkyl,
polyfluorocycloalkyl or cycloalkenyl;

wherein b is 1 or 2;

10 wherein d is an integer from 0 to 2 inclusive;

wherein each m is independently an integer from 0 to
3 inclusive;

15 wherein each n is independently an integer from 0 to
5 inclusive;

wherein each p is independently an integer from 1 to
7 inclusive;

20 wherein q is an integer from 1 to 3 inclusive;

wherein t is an integer from 2 to 6 inclusive;

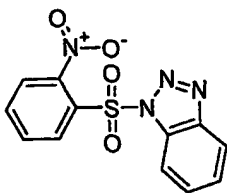
25 or a pharmaceutically acceptable salt thereof.

-302-

74. A method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound effective to decrease the consumption of food by the subject wherein the compound is selected from the group consisting of:

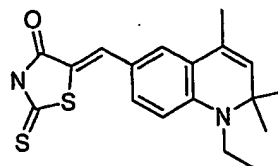
10

a)



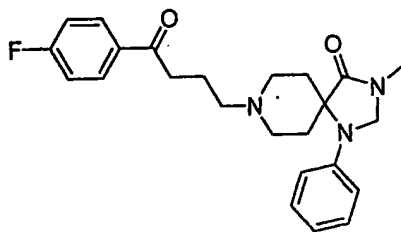
;

(b)



;

c)

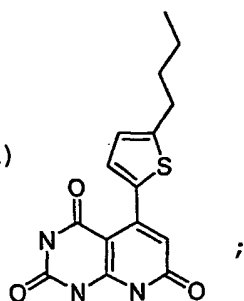


;

-303-

5

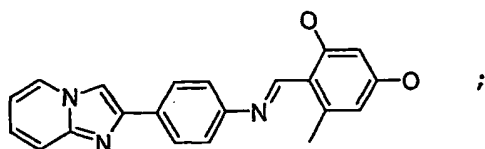
d)



;

10

e)

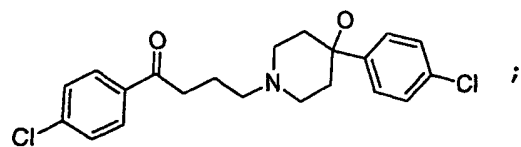


;

15

20

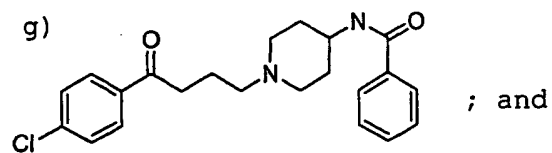
f)



;

25

g)

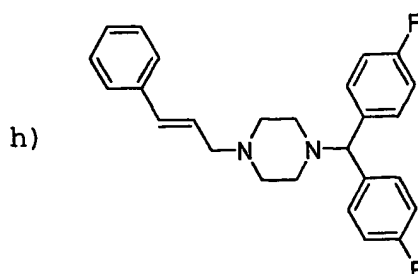


; and

30

35

-304-



5

75. A method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound of claim 34 or 38 effective to decrease the consumption of food by the subject.
76. A method of treating a feeding disorder in a subject which comprises administering to the subject an amount of a compound of claim 1, 34 or 38 effective to decrease the consumption of food by the subject.
77. The method of claim 76, wherein the feeding disorder is bulimia, obesity or bulimia nervosa.
78. A method of reducing the body mass of a subject which comprises administering to the subject an amount of a compound of claim 34 or 38 effective to reduce the body mass of the subject.
79. A method of treating a subject suffering from depression and/or anxiety which comprises administering to the subject an amount of a compound of claim 34 or 38 effective to treat the subject's depression and/or anxiety.
80. The method of claim 47, 74, 75 or 76, wherein the subject is a vertebrate, a mammal, a human or a canine.

-305-

81. The method of claim 47, 74, 75 or 76, wherein the compound is administered in combination with food.
- 5 82. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1, 34 or 38 and a pharmaceutically acceptable carrier.
- 10 83. The pharmaceutical composition of claim 82 wherein the amount of the compound is from about 0.01 mg to about 500 mg.
- 15 84. The pharmaceutical composition of claim 83 wherein the amount of the compound is from about 0.1 mg to about 60 mg.
- 20 85. The pharmaceutical composition of claim 84 wherein the amount of the compound is from about 1 mg to about 20 mg.
- 25 86. The pharmaceutical composition of claim 82, wherein the carrier is a liquid and the composition is a solution.
- 30 87. The pharmaceutical composition of claim 82, wherein the carrier is a solid and the composition is a tablet.
- 35 88. The pharmaceutical composition of claim 82, wherein the carrier is a gel and the composition is a suppository.
89. A pharmaceutical composition made by combining a therapeutically effective amount of the compound of claim 1, 34 or 38 and a pharmaceutically acceptable carrier.

-306-

90. A process for making a pharmaceutical composition comprising combining a therapeutically effective amount of the compound of claim 1, 34 or 38 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21286

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 239/32; A61K 31/505; A61P 3/04

US CL : 544/ 311, 314, 315, 316, 317, 318, 319, 320, 321, 323, 316, 330, 331, 332: 514/ 252.05, 255.05, 272, 273, 274

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/ 311, 314, 315, 316, 317, 318, 319, 320, 321, 323, 316, 330, 331, 332: 514/ 252.05, 255.05, 272, 273, 274

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6,037,354 A (PATANE et al.) March 14, 2000 (14.03.2000). See entire document.	1-33
X,P	US 6,245,773 B1 (WONG et al.) 12 June 2001 (12.06.2001). See entire document.	1-33

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" documents which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"-I" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"-X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"-Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"-E" documents member of the same patent family

Date of the actual completion of the international search

06 September 2001 (06.09.2001)

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks

Box PCT

Washington, D.C. 20231

Facsimile No. (703)305-3230

Date of mailing of the international search report

Authorized Signatory

Venkatesh Balasubramanian

Telephone No. (703)308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21286

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-33 and 47-90

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/21286

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-33 and 47-90, drawn to compound of structure shown on claim 1 wherein the core is pyrimidine ring, pharmaceutical composition, process of making the composition and method of use.

Group II, claim(s) 34-90, drawn to compound of structure shown on claim 34 and 40, with cyclohexane or benzofused cyclohexane core, pharmaceutical composition, process of making the composition and method of use.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special-technical features for the following reasons: Groups I and II relate to structurally dissimilar compounds that lack common core namely pyrimidine vs cyclohexane or benzofused cyclohexane which are not art recognized equivalent of each other. The sole feature common to the groups which does not vary is a amide group which by itself cannot be considered to define novel contribution over prior art given such fragment with substituents is known in the prior art and therefore would not constitute a special technical feature as defined by PCT Rule 13.2